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THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
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July, 1943

Howard Atwood Kelly ..... Curtis F. Burnam 1

Attempt to Induce Formation of Fibroids with Estrogen, in the Castrated Female Rhesus Monkey. Luis Vargas, Jr., M.D. 23

Studies in the Metabolism of the Human Placenta. I. Oxygen Consumption in Relation to Ageing. H. W. Wang and L. M. Hellman 31

Further Observations on the Lowering of Blood Uric Acid by Uricase Injections. Ella H. Oppenheimer and Henry G. Kunkel 40

Proceedings of the Meeting of the Johns Hopkins Medical Society 54

Book Reviews 61

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HOWARD ATWOOD KELLY

CURTIS F. BURNAM[1]

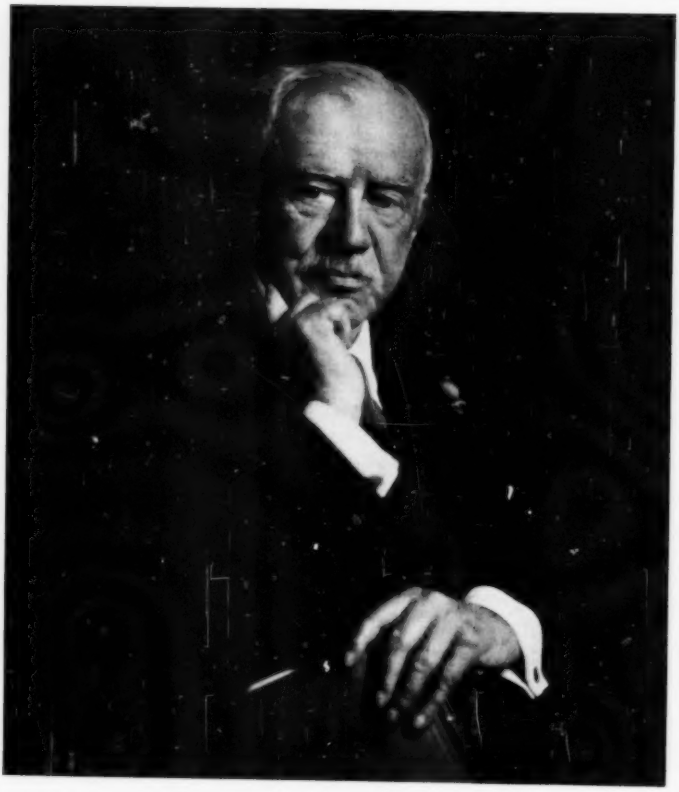
Dr. Howard Atwood Kelly[2] and his wife, Laetitia Bredow Kelly, after several years of bad health, passed to the great beyond within a few hours of each other. Both were patients at the Union Memorial Hospital, where they had been taken in emergency. The date was January 12, 1943. Had Dr. Kelly lived six weeks longer, he would have been eighty-five years old. Simple but beautiful joint funeral services were held at the Memorial Protestant Episcopal Church, of which they were communicants. Burial followed at Woodlawn Cemetery.

With the death of its first gynecologist, the Johns Hopkins Hospital lost the last member of "The Big Four," a term of affection coined and universally employed after the completion of Sargent's well known portrait. William Osler died in 1919, William S. Halsted in 1922, and William H. Welch in 1934. It may be of interest to record that Dr. Kelly always felt that Dr. Henry M. Hurd, the first director of the Hospital, who died in 1927, should have been the fifth member of this group of immortals. With Dr. Kelly's passing into history, Baltimore

[1] The author of this sketch was associated with Dr. Howard A. Kelly for many years. Receiving an internship in gynecology, he served on the resident staff in Dr. Kelly's department at the Johns Hopkins Hospital from 1900 until 1905. In 1906 he rejoined his chief at the Johns Hopkins Hospital and at his private hospital. From this time until Dr. Kelly's death in 1943, there was an uninterrupted association and collaboration in professional and many other activities.

[2] Much pertinent material has been of necessity eliminated from this sketch for the sake of brevity. The interested reader can obtain some of what has been written by reading Dr. Cullen's "Dr. Howard A. Kelly" (6) and also his fresh review, shortly to appear in the alumni magazine of the Johns Hopkins University, the manuscript of which I have had an opportunity to study. The testimonial dinner published in full in the Bulletin (3), contains a great deal directly from Dr. Kelly, and also the addresses of the speakers and letters show how he was regarded. The Faire's Classical Institute article (2) is particularly valuable from the standpoint of containing material from Dr. Kelly himself, as to his youth and the origin of his religious bent.

Those particularly interested in Dr. Kelly's work with radium can find a more complete account in the author's Janeway lecture (7).



DR. HOWARD ATWOOD KELLY

and the entire medical profession of the United States has lost one of its most colorful and magnetic personalities. However, the works he left behind him will activate and guide his successors for a long time to come.

Dr. Kelly (1) was born in Camden, New Jersey, on February 20, 1858. His father, Henry Kuhl Kelly, a successful man of affairs and a public-minded citizen of Philadelphia, later served in the Union Army during the Civil War. His mother, Louisa Warner Hard Kelly, was the daughter of an Episcopal minister, Anson Bois Hard. The original Hards settled in Connecticut (1646). The Warners were prominent in Wilmington, Delaware, in Colonial days. Thomas Kelly, Dr. Kelly's great-grandfather, migrated from Port au Doun, Ireland, to Philadelphia late in the eighteenth century. The Kuhls and Hillegases migrated to Philadelphia from Germany very early in the eighteenth century. These ancestors were active in the business, public, and religious enterprises of Philadelphia during their lives. The most outstanding, perhaps, was Dr. Kelly's great-great-grandfather, Michael Hillegas, who was born in Philadelphia in 1729. He was the first Treasurer of the United States (1776 to 1789). His business interests were manifold and included merchandizing, banking, sugar refining, iron manufacturing, coal prospecting, etc. From his earliest days he served in one public capacity after another. Exceptionally well educated, he loved music and wrote a pamphlet entitled, "An Easy Method for the Flute." He was also greatly interested in historical research. In his mental equipment, vast energy, multiple interests and physical appearance, if a portrait can be relied on, he was very much like the subject of this sketch. It is of interest that there were no doctors of medicine or scientists among Dr. Kelly's ancestors.

During the war between the States, while Dr. Kelly's father was in military service, the family resided in old Chester, Philadelphia, where the maternal grandparents lived. Even when Howard was scarcely able to comprehend, his mother, "who gave him his real start in life," and "who had convictions and tastes which he inherited, began teaching him the Bible and fostering an interest in natural sciences and books." These interests and religion had a tremendous influence on his whole life's activities. At the close of the Civil War, the father rejoined his family, consisting of the mother, the son, and three younger sisters, and they moved back to Philadelphia.

In 1867, at the age of nine, Dr. Kelly was entered as a pupil in Faire's Classical Institute (2), where he remained as a day student for six years. His own account of this period is most amusing and gives a vivid picture of the customs, games, outlook and methods of instruction of those days. He was a typical boy, full of the zest of living, a good student but "very happy when vacations came." He confessed an aversion to compositions and a real dislike for oratory. He received an excellent grounding in English, Latin and Greek, penmanship and drawing, but states that mathematics was a bug-bear. Dr. Kelly's handwriting was very legible, stylish and characteristic, and he wrote with great rapidity. His ability for sketching was equally striking and served him in good stead later in life. Many of his medical writings were done under great pressure and were not up to his best standards, as he had a real gift for writing English clearly and picturesquely. Perhaps his training in the classics also accounts for his ability to write, read and speak German, French and Spanish easily and correctly. He read the testaments of the Bible in the original Greek and Hebrew. These accomplishments were acquired after school days.

On entering as an undergraduate student at the University of Pennsylvania in 1873, he was awarded the matriculate Latin prize (3). He received his B.A. four years later. He speaks most affectionately of his professors and their influence on him, but he has written little about this period. He entered the medical school of his Alma Mater in 1877 and graduated five years later, in 1882. During the year 1880–1881, he had to interrupt his medical course on account of insomnia. This period was spent in Colorado on the O.Z. Ranch, where he acted as cowboy, postman, and doctor. On one of his cattle-driving errands he reached Grisley Gulch, Colorado, where he met and formed a life-long friendship with George Simmons, who was then practicing medicine and running a drug store in that remote outpost. Dr. Simmons was later to become the distinguished editor of the Journal of the American Medical Association. On graduation, Dr. Kelly received the Anomaly Prize, offered by the demonstrator of morbid anatomy, equally with Horace Jayne. As a medical student he was apparently much more impressed by the teachers of the scientific branches than by the clinicians, and especially by Joseph Leidy, Edward Drinker Cope and Harrison Allen. These men were all real investigators and personages

of unusual abilities. Going into clinical medicine was not Dr. Kelly's first choice, but seemed a way of earning a living and continuing his explorations into natural history.

His viewpoint as to the relative importance of vocations was changed by an interneship of a year in the Episcopal Hospital in Kensington. Contact with patients, and guidance by sympathetic and skillful chiefs brought the conviction that his "real education began in the wards and dispensary of the hospital and that richer rewards followed caring for the sick than even the greatest of the sciences could bestow." To one who knew Dr. Kelly, this change was inevitable. He was an extremely human individual who loved people, revelled in trust and affection, and rejoiced in aiding those in trouble.

Between his twenty-fifth and thirty-first years, the period of life and time now usually spent in a surgical residency, our young medical man was furiously engaged in many activities. In his own words, "after my residency it seemed better to locate in Kensington where work was waiting, than to settle down assisting the older doctors." Apparently, work began to come immediately. A two-room hospital was started on the second floor of a residence, a year later it was moved into a larger building, and a third move was made into the Kensington Hospital, which was incorporated in 1887. This is now a large and active hospital supported by voluntary contributions. In this institution Dr. Kelly was always deeply interested. Along with hospital organization, he was building up a large practice and developing new methods of abdominal and particularly, gynecological surgery. He had started his work on the diagnosis and treatment of urological conditions, then a *terra incognita*. During these years he published sixty-two papers. His skill as an operator drew visitors to his modest clinic from far and wide. Indeed, Dr. Kelly's facility with his hands, which he maintained to the end of his life, was extraordinary and this, combined with an ability to think and improvise on a moment's notice, marked the great surgeon. To this was added a thorough knowledge of gross anatomy and a willingness to go back to dissections time and again.

In addition to knowing the gynecologists of his home city and their work, he met and observed all the others in the country. He never saw Marion Simms operate, but was greatly influenced in his plastic surgery by Thomas A. Emmett. He found time for three visits to Europe in

this period, tremendously broadening his vision and creating many new friends in England, Scotland, Germany, Austria, France, and Switzerland. These leaders in gynecology in many lands became regular correspondents, and some of them returned his visits. The author of this sketch was greatly impressed many years later (1901–1902) by the open sesame given him on announcement that he was an assistant of Howard Kelly. Not only was access immediately given to the clinics, but to the homes of famous men.

Dr. Kelly's first trip abroad (old connotation; it means something quite different to-day) was in 1886, the second in 1888, and the third in the summer of 1889. On June twenty-seventh of that year he was married in the Marienkirche in Danzig to his life's helpmeet, Laetitia Bredow, daughter of Dr. Justus Bredow of Berlin.

At the period under review, the rudimentary condition of surgery is now difficult to comprehend. Anesthesia was still in its infancy. Many of the leaders in obstetrics and gynecology still opposed the ideas of sepsis and those who did not were dominated by the necessity for antiseptic procedures, rather than asepsis. Bacteriology and cellular pathology were just beginning to take hold of the minds of clinicians and were being translated into effectual applications in the wards and operating rooms. To those who are interested, an excellent picture of the conditions then existent can be secured by reading two of Dr. Kelly's papers, "History of Gynecology in America" (4), and his "History of American Gynecology, a Brief Review" (5).

In connection with his work, Dr. Kelly was fortunate in securing consultations with some of the leading men in Philadelphia and particularly, with William Osler. He modestly says, "What interested Osler most was, I think, my good library of the medical classics," of which even at that time he had collected a number of rare volumes. Dr. Osler's opinion of the operative ability of the "Kensington Colt" and of his possibilities as a professor of gynecology and obstetrics, is shown in a note to Dr. Henry M. Hurd (6).

There can be very little doubt, and Dr. Kelly always felt that his call to the Johns Hopkins Hospital and University was due to the activities of the professor of medicine in behalf of the Hospital, University, and the young gynecologist. As a matter of fact, he was appointed associate professor of obstetrics in 1888 at the University of Pennsylvania.

In the fall of 1889 there was a preliminary visit, which permitted a view of the Johns Hopkins Hospital and an opportunity to meet the men with whom he was to be associated for so many years. He had an interview with President Gilman, who outlined the high aims and ideals of the new institution in a way that "fired his imagination." He returned that same fall, having accepted the professorship of obstetrics and gynecology in the Johns Hopkins University, and the directorship of these departments in the Hospital. He first lived on Broadway near the Hospital, then opened an office on Charles Street, where he remained until 1892.

In 1892 he removed his residence to Eutaw Place and took over some houses nearby in which his first resident, Hunter Robb, had started a private hospital. The facilities for private patients at the Johns Hopkins Hospital at that time were limited and available only to the heads of departments. Dr. Robb had received a call too, and had accepted the chair of gynecology and obstetrics in Western Reserve University in Cleveland. Almost certainly, it was to help Dr. Robb that he started "The Sanitorium." This name was changed to "The Howard A. Kelly Hospital" and it was incorporated in 1913. Since Dr. Kelly's retirement in 1940 it continues as The Kelly Clinic.

A glance through his Bibliography, prepared by Minnie Wright Blogg and published in the Johns Hopkins Hospital Bulletin as an appendix to Dr. Cullen's tribute (6), referred to above, shows clearly that his interests were not extensive in obstetrics. Only five papers out of sixty-two written by Dr. Kelly were written on this subject, and one of these was the report of a caesarian section in 1888, "the first successful one in Philadelphia for fifty years." Nevertheless, Dr. Kelly was a trained obstetrician and took cases for a time in his private practice.

Dr. Kelly's teaching during the first few years was limited to post-graduates who were attracted from far and wide by his and his distinguished colleagues' reputations. Until the opening of the Medical School in 1893, there were no facilities in the Hospital for taking care of obstetrical patients. The correction of this situation became imperative then and the development of this most important branch of medicine was practically delegated to Dr. Kelly's associate, Dr. J. Whitridge Williams. In 1899 the two departments, gynecology and obstetrics, were separated, Dr. Kelly relinquishing the professorship of

obstetrics in the University and the departmental headship of obstetrics in the Hospital to Dr. Williams.

The gynecological service was physically represented at that time by old Ward O for negro women, old War H for white women, and Ward B for private patients. The first operating room was in Ward B, which is still a part of the Wilmer Ophthalmological Clinic. In 1892 the new operating room, then called B, was built; and in 1897 through a generous donation by Dr. Kelly, it was enlarged, thus affording a lecture room and a cystoscopic room. The outpatients were seen in the old dispensary building, certain rooms being used for the medical clinics in the mornings and for gynecology in the afternoons. Dr. Welch provided a room in the old pathological building where gynecological pathology was established and developed by Dr. Thomas Cullen, Dr. Kelly's associate. All of these buildings have been torn down and replaced by the present commodious modern structures.

The teaching from the outset was modern, marking a complete reversal from the methods then current. Didactic lectures were replaced by clinic examinations, demonstrations, and actual contact with patients. This direct approach in instruction was, of course, not confined to gynecology, but was the keynote of teaching in all departments. It represents perhaps the greatest contribution to medical education in American history.

The procedure in dealing with a patient in the Department of Gynecology was as follows. One of the assistants in the Department summarized the clinical history of the patient, as well as the objective findings in the case; then, when feasible, he permitted the student to examine the patient under an anaesthetic, and to make the diagnosis. The patient was then immediately transferred to Dr. Kelly for operation, during which procedure Dr. Kelly would pause from time to time to demonstrate the conditions found and explain the steps of the operation. Opportunity was given the students to follow subsequent developments on the wards and in the laboratories. Considerable color and drama were added in the operating room by the daily presence of many visiting surgeons, who asked questions and made suggestions.

Always giving great freedom to his staff, Dr. Kelly must have been greatly aided by the young men associated with him, Robb, Staveley,

Russell, Clark, Cullen, Ramsey, Williams, and others, in the organization of the Department from the standpoints of teaching, investigations, and care of the sick.

Dr. Kelly's personal contributions were outstandingly researches in operative gynecology and gynecological urology. This entailed conceptions and applications of many new procedures. In the actual manipulations he had the great natural advantage of extraordinary manual dexterity. Employment of unusual postures, construction of special instruments, careful recording of everything, had to be carried out. All of this is old now, but it was new and fresh then.

Perhaps the elaboration and application of the open-air Kelly cystoscopic methods furnish the best example of his work. From almost nothing the armamentarium and methods of gynecological urology as it is today came into existence in a few years. Again, in this enterprise Dr. Kelly was most fortunate in enlisting his associate, Guy Hunner, who has continued developing and popularizing this gynecological subdivision to this day.

Dr. Kelly all his life was very open-minded and inclined to promptly adopt methods and means which promised simplification and improvement in the clinic. Undoubtedly, Dr. William Halsted's fundamental researches on how to obtain aseptic conditions influenced greatly the operating room technique. However, so far as the Johns Hopkins Hospital is concerned, the preparation and use of absorbable sutures are due to the Gynecological Department. The introduction into the operating room of nitrous oxide as a convenient anaesthetic is also due to Dr. Kelly. Cullen's frozen section method of tissue diagnosis at the operating table is another child of the Department. In the employment of radium and roentgen radiation, and of electric coagulation and fulguration methods, notable advances were made in gynecological therapy, which likewise exercised profound influence in all the surgical and medical specialties.

In the Hospital's medical society, its historical society, and the nurses' association, Dr. Kelly had a profound and lively interest, as is personally known to the author of this sketch, and is amply verified by the transactions of these societies, which are published in the Hospital Bulletins.

This interest in medical history, dating from Philadelphia days, con-

tinued all Dr. Kelly's life. One of his last contributions was "Reminiscences of Howard Kelly on the Development of Gynecology" (10). He donated his valuable and large collection of medical classics to the Welch Library, and to the training school for nurses went his Florence Nightingale letters. In addition to writing a number of short biographical sketches (6) and historical essays, he published "Walter Reed and Yellow Fever" in 1906 and in 1912 an encyclopaedia of American medical biographies. Both of these books were exceedingly well executed and involved a great deal of labor and time.

From early childhood "his mother's influence" led to an intense interest in the natural sciences. He was familiar as few laymen are, with astronomy, geology, botany, and reptilia. The delving into these fields replaced the more conventional recreations of most men and afforded a marvelous opportunity for outdoor as well as study activities.

He was really an authority on North American snakes and as early as 1899 wrote a paper on "The Recognition of Poisonous Serpents of North America." This interest caused not a few of the uninformed, who saw him handling poisonous snakes, and even some of those who never saw the snakes, to believe that something was abnormal in his tastes if not in his mind. Dr. Kelly was partly responsible for this attitude, for he knew the general aversion to snakes and was always greatly entertained at the reactions of his visitors. He was also a specialist in mycology, particularly mushrooms. He employed L. C. C. Krieger, a splendid artist, for a number of years in the collection and painting of specimens and the development of a splendid library. All of this material was given as the Krieger Collection to the University of Michigan (3). In 1914 Dr. Kelly published an interesting booklet, "Some American Medical Botanists in our Botanical Nomenclature."

Through his association with Max Broedel, Dr. Kelly indirectly exerted a profound influence on medical illustrating. One might almost say that Broedel revolutionized this important field.

Dr. Kelly was a facile sketcher. The early gynecological histories at Johns Hopkins Hospital, as well as those at his private hospital, are filled with his drawings. He began taking photographs through the aid of Mr. Anthony S. Murray, an enthusiastic amateur photographer and friend, almost at the beginning of his work in Baltimore. Also, lantern slides for teaching were made and used. In 1908 he produced the first

of a series of stereo-photographs of operations. There followed 42 sections in all. In this work, which involved visiting many clinics in North America and England, he was aided by Dr. Cecil Vest (11). Garrison speaks of these photographs as a permanent record of current surgical procedures (1910–1913) (6). To Dr. Kelly the securing of these photographs was a delightful educational and social diversion.

Max Broedel joined Dr. Kelly in 1893 and remained with him until he became the director of the Department of Art as Applied to Medicine of the Johns Hopkins University in 1911 (3). Broedel was not only a magnificent artist, but an anatomist of the highest order. Through him a number of artists, notably Herman Becker, 1895, and August Horn, 1898, joined the gynecological staff. All of them were subsidized by Dr. Kelly. Where Broedel thought necessary, he was encouraged to and would work for weeks at a time in anatomical studies in order to clearly and accurately draw a single picture. Dr. Kelly's rough sketches helped the artists complete their sketches made at the operating table. Dr. Kelly was constantly in touch with the art staff, and things were done over and over again until satisfactory results, in the opinion of all concerned, were obtained. Broedel's anatomical studies and drawings added greatly to the value of some of Dr. Kelly's publications, but without the freedom and help given him in his formative years, Broedel might never have become the remarkable illustrator into which he developed. Together, the pair constituted a great team for the work they were endeavoring to do.

I will not dwell on Dr. Kelly's publications. They were very numerous. Dr. Thomas S. Cullen, his successor, has done this admirably. To Dr. Cullen's review is appended a bibliography prepared by Minnie Wright Blogg, librarian of the Welch Library (6). In all there were 485 titles including books, pamphlets and journal articles. From 1919 to 1938 he made sixty additional medical contributions to journals, wrote sections in several systems of gynecology, revised some of his earlier books, and wrote a book with Dr. Grant E. Ward, "Electrosurgery," 1932.

During his entire life, Dr. Kelly wrote continuously for many religious journals, and in 1925 brought out a book, "A Scientific Man and the Bible."

Some of Dr. Kelly's books are not in the ordinary sense, text-books,

but are monographs, embodying his experiences and planned investigations extending over many years. This is notably true of his "Operative Gynecology," his and Elizabeth Hurdon's "Vermiform Appendix," his and Thomas S. Cullen's "Myomata of the Uterus," and his and Curtis F. Burnam's "Diseases of the Kidneys, Ureters and Bladder." These books are reference stores and in many ways are still as fresh as when they were written many years ago.

Few men more clearly appreciated the values and necessity of scientific and progressive associations in relation to the dissemination of knowledge, the stimulation of research, and the elevation of medical practice and standards. Most of his younger associates can, I venture, recall his encouragement and even, in some cases, prodding, to the end that they join, attend, and take an active part in society meetings. He knew that journals were indispensable and must be supported; and that they were worthwhile, as a rule, in proportion to the support given them. He subscribed to many journals and urged others to do likewise.

Dr. Kelly, both as to societies and journals, took, himself, the medicine he prescribed for others. He never sought authority in the active management of the societies of which he was connected, but preferred the position of an independent active member. Possibly a feeling of political inadequacy, but certainly the pressure of more urgent responsibilities, was at the bottom of this attitude of gladly delegating to others with more time and, as he said, aptitude for such duties as fall to officers of medical societies.

Never apparently impressed when he was the recipient of some token of appreciation such as an honorary membership in a distinguished scientific society, or an election to office in a professional society, or on receiving an honorary degree from a university, he seemed to feel that he had not earned the distinction, but attributed its arrival to the kindness and consideration of the donors. His evident pleasure was in sharp contrast when some friend or associate was in the receiving position, and he was likely to say his work had been outstanding.

It was inevitable that one who had accomplished so much as had Dr. Kelly, should have had bestowed on him definite marks of recognition by his peers. He was the recipient of many such tokens of esteem. To those interested in knowing exactly what they were, a complete

list is to be found in the obituary notice in the Journal of the American Medical Association (12).

Dr. Kelly was president of the Southern Surgical and Gynecological Association, 1906, and of the American Gynecological Association, 1912. He delivered the Hunterian Lecture in London, 1928, at the occasion of the celebration of the two hundredth anniversary of the birth of John Hunter. The degree of LL.D. was conferred on him by Aberdeen University, and by Washington and Lee in 1906; and by Johns Hopkins University in 1939.

After serving for three decades (1889–1919) as Chief Gynecologist and Professor of Gynecology, Dr. Kelly resigned but accepted the title of Emeritus Professor. He continued to watch with interest the developments in the Department and in the Hospital as a whole, and especially the Nursing School. Occasionally by invitation he operated for the students, the last time on January 10, 1938, when he was close to eighty years old.

Dr. Kelly had nearly ten years ahead of him before he was to attain the three score and ten retirement age prescribed by the University for its professors. His mind was as keen as ever, his physical health perfect at the time of his resignation. Undoubtedly, although his own department was not directly involved, it was the change to the full time clinical professorships that chiefly motivated him to take this step. He was not convinced that the change was a step forward. On one occasion he said to the author of this sketch, "I don't understand it, but they all feel (his colleagues) that it is wonderful, and I am sure that my resignation will give them a better chance to develop the plan." Welch had always been full time. Halsted and Williams gladly made the change from their previous status. In the several newly organized departments, the full time system was instituted at their inception. Then, too, his great and much admired friend, William Osler, had voluntarily resigned at approximately the same age. Dr. Kelly felt, too, that his specialty from the standpoints of operative surgery and the known diagnostic measures, was firmly established; that further great advances would have to be made along entirely new lines and approaches.

In addition to all this, Dr. Kelly's extra-mural activities had steadily grown. His interest in public, social, moral, and religious problems,

always strong, assumed greater proportions. Then, too, through the Howard A. Kelly Hospital new vistas of therapy, not only in gynecology but in many fields, were being explored and many finds located. These statements are based on memory of conversations held with Dr. Kelly at the time he contemplated resignation. He ever afterwards felt that the step taken was a wise one, and so far as I know, he never regretted it.

After his retirement, Dr. Kelly continued his professional activities at the Kelly Hospital. This institution, organized in 1913, took over the physical property of the Sanatorium, which he had started in 1892. At the Sanatorium Dr. Kelly operated between 6:00 and 8:00 A.M., before going to Johns Hopkins. He was assisted for some years by Dr. William Wood Russell, and later by Dr. Guy L. Hunner, while Dr. Thomas Brown and later, Dr. Warren Buckler gave the anaesthetics and supervised the post-operative care of the patients. When I joined him in a similar capacity in the spring of 1906, I found an equipment, in instruments and appliances for diagnosis and operative procedures, many of them devised by Dr. Kelly, superior to anything I have ever seen in any gynecological clinic. The accumulation of this armamentarium represented not only a great financial outlay, but evidently was the fruit of prolonged thought and experience in clinical applications. A diagnostic x-ray apparatus was, I believe, used at the Sanatorium some years before any other Baltimore institution employed this indispensable diagnostic aid. The laboratory work, except for urinalysis and blood counts, was done at Johns Hopkins Hospital.

At this period, Dr. Kelly had a small tube containing a few milligrams of radium, which he had purchased several years previously (7). This preparation had some value in treating tiny skin lesions, but was inadequate for gynecological use and was almost a toy. It was very rarely used. In 1909 or 1910, Dr. Kelly's interest in radium once more was awakened by contact with Dr. Louis Wickham of Paris, France, who visited Baltimore and demonstrated his findings in radium therapy. Through Dr. Wickham, early in 1911, enough radium was obtained to begin treating gynecological cancers and other conditions. In the same year was set up our first radon apparatus. From the very beginning, the results of clinical applications were striking. Dr. Kelly visited England and France in 1911 to study the situation, made many

valuable contacts, and purchased a small additional amount of radium. I visited England, France, Germany, and Austria in early 1912, again in 1913 and 1914, and secured considerably more radium. It seemed to us that a gram of radium would suffice for treating deepseated lesions. More than this amount was secured by purchase in early 1913.

In the meantime, it was found that the accommodations and equipment of the old Sanatorium were inadequate to take care of this new work. Additional buildings were added; laboratories for doing necessary pathological, bacteriological, chemical, and physical studies, were established; and the personnel for managing them was brought together. In that same year, 1913, the first apparatus for deep x-ray, the first by years in Baltimore, and one of the very first in America, was set up in the small clinic and hospital, which had been incorporated as the Howard A. Kelly Hospital. The clinical results obtained with radium during 1912 and 1913 seemed so much superior to those obtained from x-ray, that it was felt that there must be a qualitative difference in favor of short wave lengths in their biological effects. There are differences, but we know now that they are much less important than they then seemed. A few publications and demonstrations made by members of the new hospital as to the possibility of radium in cancer treatment, led those in authority in the Bureau of Mines in Washington to visit Dr. Kelly and Dr. James Douglas of New York, in reference to a project for mining and developing economical methods of extracting radium from American carnotite ore, which was found in Colorado and Utah. The result of a number of conferences was the establishment of the National Radium Institute in 1913. From this project, the Howard A. Kelly Hospital secured several additional grams of radium, as also did the General Memorial Hospital in New York City through Dr. Douglas's generosity to that institution.

The Bureau of Mines published (8) an account of its activities in connection with the Radium Institute's work, and the author has sketched the general history of the Howard A. Kelly Hospital's relationship to the development of radium and x-ray therapy during this period (7).

With the great increase in the number of patients applying for treatment, not only for gynecological but many other conditions, the

Hospital accommodations were inadequate, and much wider familiarity with general medicine and surgery became imperative.

A workable follow-up system was devised; the medical, nursing, clerical, and technical staffs were greatly expanded.

As the increase in patients was due to those seeking radiation therapy, two courses were open so far as hospital accommodations were concerned; the first, to build a larger hospital, the second to use all the radium necessary, often all we possessed, and treat one patient at a time. The second plan was adopted, as it was immensely more economical, much easier on the patient, and very efficient from the standpoint of dosage accuracy.

This concentration of the radium necessitated, for adequate protection of the Hospital personnel, the development of new methods which were at variance with those employed elsewhere. A similar set-up would, I believe, be more generally followed if all our great hospitals and medical centers were adequately supplied with radium.

At any rate, this plan made it possible for the Hospital to carry on a major part of Baltimore's and Maryland's radiation therapy, and all that of the Johns Hopkins Hospital, over a period of many years. This was done under great financial strain, as the Hospital had no income except that received from private patients, and all patients, rich and poor, were accepted and were given the same care. Even a greater pressure, in lengthening hours of work and in increasing efficiency and energy on the part of the personnel, was necessitated by this effort to serve the community. The work could never have been accomplished except for the help of the staffs and administrations of the Baltimore hospitals, and notably that of Johns Hopkins.

As a direct result of the set-up, the Kelly Hospital was the first to use radium in packs at appreciable skin distances, to construct and use a teleoradium apparatus, and to establish a large radon plant. All of this was accomplished in 1913 and early 1914.

It may be of interest for future readers, who did not know Dr. Kelly, to describe his physical characteristics. He was of medium stature, approximately five feet, eight inches tall, very muscular, possessed of extraordinary coordination. His hands were strong and well shaped, and gave the impression that he belonged to the athletic type of man. He was neither very blond nor very dark; his head was large and well

shaped. His face, mobile and expressive of his emotions, was lighted by gray eyes that twinkled with intelligence and amusement, depending on the thoughts of the moment. There is an oil painting of Dr. Kelly in the Woman's Clinic at Johns Hopkins Hospital; and also, the Sargent portrait of The Big Four hangs in the Welch Library. In the biography in The Faire's Classical Institute, there are several reproductions of photographs, one when he was twelve years old. In the "Dr. Howard A. Kelly" of Dr. Cullen, there are two photographs, one as he was when his duties at Johns Hopkins were first assumed, and the other as he appeared at the time of his resignation. There is published here a photograph taken when Dr. Kelly was nearing his eightieth birthday.

Until he reached the mid-forties, Dr. Kelly was very slender and young looking. When I was an intern we occasionally had some ward patients who came to Baltimore for Dr. Kelly's personal ministrations and were particularly anxious to avoid a neophytic gynecologist. Some of them, on meeting the great man, were with difficulty persuaded that they were not being deceived and defrauded by the scalawag residents. In middle life he gained a great deal in avoirdupois, much to his dislike. He went to a celebrated medical confrere, who prescribed a diet; and as he did everything else, he followed directions with a vengeance and lost fifty or more pounds in a short period. He felt a great deal better and was inclined to show his associates by unusual activity that they might follow the same program to their benefit. Unfortunately, this urge may have led to a severe injury of his cervical vertebral column, which he received following a high dive from a thirty foot height. He had miscalculated the depth of the lake into which he dived. This was only a few months after his dieting, and he was at his camp in Canada. As a result of this injury, Dr. Kelly never looked or felt quite the same.

Although he was serious when discussing or conversing about vital questions, of which there were many in his list, few persons had a keener sense of humor than did Dr. Kelly, and he was particularly amused when the joke was at his own expense. During my early days at the Hospital, one of his children, a little boy, was brought into the Hospital for some minor ailment and was visited by a young man whose mother was to be operated on. The young man asked the small boy if he was

being prepared for operation. "My, no!", was the reply, "Everyone operated on here dies." Dr. Kelly, when he heard of this from the visitor, laughed heartily, and so far as was known, never corrected his impish small son.

Dr. Kelly was fond of harmless mystifications and pranks, and was an eternal small boy himself.

For many years he did not urge me to follow in his religious footsteps, but faith, and work showing faith, transcended all other things with him. One day when he was very ill, only a few months before his death, he asked me to be more active in religion. On my replying that I would think his suggestion over, he retorted with the amused twinkle in his eyes, "Well, doctor, how old do you think you ought to be to take this stand?" We passed on then to other topics.

Extremely hospitable and most courteous and polished in his manners, Dr. Kelly was a wonderful host. In the early days of my association with him, there was rarely a time when at his breakfast table, in addition to Mrs. Kelly and his nine children, there were not several guests. Only a few steps from the Hospital, I often dropped in to ask some question, and the welcome received from all made me feel a member of the family.

An English woman secretary, about this same time, came to assist him in his library and introduced the afternoon tea custom. Dr. Kelly loved this and continued it ever afterwards. One found at his teas persons of every kind and description. His acquaintanceship, if not to say friendship, was enormous, covering people of every profession, business, creed and occupation. On one occasion, when I visited him at this hour, he was having a lively interview with Francis Wilson, the stage comedian, a man of culture and real ability. At the time, Dr. Kelly was very doubtful as to the morality of stage people. Wilson was so convincing and sincere in his defense of the theatrical profession, that he changed Dr. Kelly's views. As a matter of fact, the chief was always open-minded and willing to change his mind when presented with the opinions of others, whom he felt knew the facts better than he did.

Another strong characteristic was Dr. Kelly's avoidance of all gossip. I never heard him say an uncomplimentary thing of one of his associates. His admiration and affection for his colleagues in the

University were sincere and very great. He had definite opinions and was able to defend them ably; but no matter how much his adversaries might interject personality into a debate, he neither put them nor himself on trial, but held fast to the questions under consideration.

I have already spoken of Dr. Kelly's remarkable industry. He was always doing something, except when sleeping. This probably started in early youth, but certainly existed in the entire period with which I personally know about. Everyone who knew him was familiar with his small pocket diary and fountain pen. He was always making notes and having people write their names in this diary. These diaries, dating from boyhood to his death, should some day form the basis for a real biography. This habit of working without relaxation made ordinary social intercourse almost impossible. He enjoyed people so much that this was in my opinion a real misfortune.

Frugal in purely personal expenditures, his generosity in aiding people and causes in need, was spontaneous and unusual. He rarely asked advice about a benevolence, and apparently forgot it when it was once accomplished. As a consequence, even one as close to him as the author knew only by chance, if at all, what he was doing.

Dr. Donald Guthrie of Sayre, Pennsylvania, gives Dr. Kelly the credit for establishing the first boys' camp in America, in Rickett's Glenn, Luzerne County, Pennsylvania. Guthrie's address of welcome to the American Gynecological Society at its 1942 meeting at Skytop, contains a graceful tribute in reference to this pioneering in a field removed from medicine.

Quite by accident, I learned of another such project, as a result of an inquiry as to what had become of a man who had served as an intern with me. It developed that early in his career Dr. Kelly had established a rotating fund to enable needy students to obtain a medical education. He carried this on for years and made possible medical training to a number of young men. It would be interesting to know how many there were so helped, and what they have accomplished in their after lives.

Deeply concerned in the social, moral, and economic uplift of the poor and downtrodden, and firmly believing that lasting betterments could only come when founded on a firm Christian basis, it is certain that Dr. Kelly's greatest charities were in support of such philanthro-

pies as "The Lighthouse" in Philadelphia and Christian missions in America, but particularly in foreign lands.

Known as a public-minded citizen, with no personal axes to grind, he was greatly admired and respected by the leading political figures of his day. It must be confessed, however, that they and many other fine citizens did not always see eye to eye with him. Impulsive, full of both moral and physical courage, he vigorously threw himself into many reform movements. One of the first of these was to secure better and fairer election conditions in Baltimore. His experience as a poll-watcher in the Marsh Market district has been often described. He vigorously fought commercialized vice by word of mouth and by pen, and saw its abolition in his adopted state. He espoused the prohibition movement, rejoiced when the amendment came, but finally acknowledged that it failed to fulfill the purpose for which it was devised, namely temperance. Somewhat doubtful as to the improvement which would result from giving women the right to vote, he nevertheless threw himself into the women's suffrage movement because he felt justice demanded such a reform. Religious as well as aesthetic considerations influenced his distaste for the birth control movement, which he opposed. He was very active and spent a great deal of time and energy in the Lord's Day Alliance movement. It was, I believe, the opportunity that traveling from town to town gave him to present his faith to multitudes of people, rather than to maintain restrictive Sunday laws, that kept this interest at such a high pitch for so many years.

Dr. Kelly looked forward to his vacations with a great deal of pleasant anticipation. Most of his summers were spent at his camp, "Indian Point," on Lake Ahmic, Ontario, Canada. He secured this location in 1891, and its attractive features can be found in Dr. Cullen's description, as well as in the Birthday Dinner record. During my residency at Johns Hopkins Hospital, I spent one summer vacation at this attractive spot.

Summer vacations to Europe might have been more frequent, except that seasickness made the ocean crossings a veritable nightmare. Winter vacations were also frequently taken for several years to the State of Oaxaca in Mexico, where he had mining investments. This was in the time of Porfiro Diaz, whom Dr. Kelly knew well. A great deal of interest was added to these trips by his observation of the

Indians and visits to prehistoric ruins. Later, his winter visits were to Florida, where he botanized and delivered sermons in many localities. He visited congenial friends, who went with him from place to place by automobile.

Dr. Kelly told me once that in his young days he was an ardent hunter, but gave it up because of his "dislike of killing wild things." Although he was supplied with unending fishing tackle, during my summer with him I never saw him take up a rod. I think that fishing was too slow a sport for him. He was a magnificent swimmer and an expert canoeist. He particularly enjoyed a week's camping out, traveling by canoe and effecting overland portages from lake to lake.

I have perhaps already dwelt enough on Dr. Kelly's religious side. It was an enduring passion and transcended everything else with him. His knowledge of the Bible, his constant companion, was profound. He was not bound by any church forms or tenets; but not antagonistic to them, he was at home in any church. It is true that he deplored modernistic trends and belonged to the conservative group, which exists in every denomination and creed. His own writings afford the best source for understanding his views. Dr. H. Chisholm contributes in an obituary essay (9) in the Sunday School Times a religious man's estimation of Dr. Kelly.

Dr. Kelly and Mrs. Kelly are survived by nine children, a number of grandchildren and some great-grandchildren. A son, Edmund B. Kelly, is the only doctor in the family. He is a member of the staff of The Kelly Clinic, the successor of the Howard A. Kelly Hospital, and is at present serving with the Johns Hopkins Unit No. 118 in the Southwest Pacific area. A grandson and namesake, a warplane pilot, perished in the Tunisian campaign, dying a few weeks before his grandfather. The news did not reach the family until after Dr. Kelly's death.

An appraisement of Howard Atwood Kelly must, of necessity, be left to those who will have the advantage of a historical perspective. The temptation, however, to indulge in prophesy cannot be entirely resisted. I have not mentioned that he was beloved by all who assisted him. There is not one of them who does not owe a great deal of his success to Dr. Kelly's influence and help. A list (3) of his residents at Johns Hopkins contains the names of men who are among the present leaders in gynecology in this country; and of those no longer living,

many attained great prominence in this specialty. His influence extended far and wide through the entire profession of medicine.

His part in extending the fame of the Johns Hopkins Hospital, and thereby promoting its development, is gracefully and beautifully expressed in a letter written by his famous colleague, Dr. William H. Welch, who was on his own deathbed. The occasion was the Birthday Celebration. No one can question that Dr. Kelly was one of the important builders of the Johns Hopkins Hospital and Medical School. His great originality, his persistent constructive investigations, his publications by which he imparted his findings to the medical profession, all mark the great man. It is my sincere opinion that his name will go down in history as a great pioneer, as an eminent medical man, and as one of the greatest of gynecologists of all time. As it was stated in the beginning of this essay, the cessation of his activities is a great loss to the profession, but his influence will long be with those now living, and those gynecologists to come.

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ATTEMPT TO INDUCE FORMATION OF FIBROIDS WITH ESTROGEN, IN THE CASTRATED FEMALE RHESUS MONKEY

LUIS VARGAS, JR., M.D.[1]

From the Department of Embryology, Carnegie Institution of Washington, Baltimore

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Because of the work of Nelson (16) and of Lipschütz and co-workers, who found it readily possible to produce fibroid tumors in guinea pigs by prolonged administration of estrogenic hormones, it was thought worth while to make a comparable experimental study in the monkey. This experiment is not superfluous, in spite of several previous studies of the effects of prolonged estrogen treatment upon monkeys (1, 3, 6, 17, 21), and even in spite of the very extensive experiment by Hartman, Geschickter and Speert, of which a brief report was given in 1941 (5), and which is partly still in progress in the Carnegie Embryological Laboratory. In this investigation, in which very large quantities of estrogenic hormones have been given to monkeys for long periods of time, no fibroids or other tumors have been reported. It is true, however, that this experiment, like the others mentioned, did not have quite the same end in view as that to be reported here, and that the procedure was not comparable in every detail with that by which the estrogen-induced fibroids are produced in the guinea pig.

Lipschütz and co-workers (12) have shown, for example, that the highest degree of tumor formation is obtained in the oöphorectomized guinea pig. There seems to be a protective effect of the ovaries against tumor formation (9). In the experiment of Hartman, Geschickter and Speert only one of the whole series of female monkeys was castrated, and this animal has not yet come to autopsy.

Lipschütz, Rodriguez, and Vargas (10) have shown that continuity of estrogen administration is important for the production of tumors in the guinea pig. Discontinuous estrogen treatment does not result in the appearance of fibroids. The necessary continuity of adminis-

[1] Guggenheim Fellow, 1941–1943, from Santiago, Chile. Present address, Universidad Católica de Chile, Santiago de Chile, S. A.

tration was obtained by subcutaneous implanation of tablets or pellets of the hormone, and this led to the genesis of fibroid tumor tissue at a regular rate (11, 13).

In guinea pigs the result of the treatment is a fibroid reaction of greater or less degree, occurring chiefly in the peritoneal and subperitoneal tissues of the abdominal cavity and the pelvis. Since this reaction exhibits itself in three forms of increasing intensity and extent, namely fibrosis (19), disseminated miliary nodules (20), and fibroid tumors (fibromata and fibromyomata (8,15) it is essential to search the experimental animals carefully for reactions of all these types, in order to detect or exclude a response to the estrogen treatment.

It was therefore determined to carry out a small experiment in which two points were fundamental: 1) to make the experimental conditions as closely similar as possible to those which yielded positive results in the guinea pig, and 2) to terminate the observations by careful systematic examination of the whole peritoneum.

EXPERIMENTAL

Four castrated female rhesus monkeys weighing 3560 to 4840 grams received tablets of α-estradiol.[2] The tablets were prepared with the machine of Vest and Howard (18) without close control of the degree of compression. The tablets weighed 70 to 112.7 mgm. Each animal received one tablet, implanted in the subcutaneous tissues of the anterior abdominal wall. At the time of the oöphorectomy 2 females were immature (no. 729 and no. 730) and 2 were mature (no. 185C and no. 703). Animals 729 and 730 were castrated on January 2, 1941, 703 in February, 1940, and 185C in December, 1938. The tablets of estradiol were implanted in all four monkeys on January 21, 1941. Some idea of the relative effect of the estrogen was obtained throughout the period of experimentation by observing the skin color of the sexual region and the level of the vaginal desquamation. The period of treatment ranged from 69 to 290 days (see table 1). No. 729 died for reasons not revealed by autopsy. Laparotomy was performed in monkey 730 at 264 days of treatment. At the same time biopsies were taken from the vagina, cervix and mammary gland of this and the other two living animals. No. 730 died of early miliary tuberculosis, although an x-ray of the thorax was clear 3½ weeks before death. Nos. 185C and 703 remained in good health and were killed to terminate the experiment.

[2] The estradiol was generously supplied by Ciba Pharmaceutical Products, Inc.

RESULTS

Estrogenic effects. The implanted hormone produced a prolonged and continuous estrogen effect, as indicated by the state of the sexual skin, vagina, uterus, and mammary gland. The color of the sexual skin promptly became and remained high, ranging between 5 and 9 on the Corner scale used in this laboratory (2), in which the maximum reading is 10; and the vaginal desquamation, as measured by the technique of Hartman used in this laboratory (4), was also constantly fairly high, reading from 14 per cent to 20 per cent. In animal 730 the tablet of estradiol was eliminated about 10 days before the end of the experiment, when it was very much diminished in size. The estrogen effect, however, did not decrease after the elimination of the tablet and no genital bleeding was observed. In animal 703, after about 180 days of treatment, the vaginal sediment started decreasing from 10 to 14 per cent to a trace. At 200 days of treatment the vaginal washings were clear and the color of the sexual skin also decreased. Nevertheless, no vaginal bleeding was noted. At autopsy it was found that a total absorption of the tablet had occurred.

Microscopic examination of the mammary gland showed marked development in 729 and 730, less intense in 185C and 703.

The uterus was enlarged in all the animals. Microscopic examination showed in all four a slight development of the endometrial glands of the corpus uteri, and in animal 185C the glands were in places cystic.

In animals 729 and 730 there was epithelial squamous metaplasia of the cervical region of the uterus and of its glands, as reported by other workers (1, 3, 6, 17, 21). In these two animals the metaplasia was very pronounced and involved a large part of the cervix, but it did not spread over the corpus. In animal 185C, which showed a full estrogen effect, the squamous metaplasia did not occur and in only a few places in the cervix was there a tendency to advanced stratification of the epithelium.

Fibroid reaction. In animals 730 and 185C there was diffuse fibrosis of the myometrium, especially pronounced around the cervix, but in animal 703 this was almost absent. In no. 730 the cervical fibrosis was so intense that it was difficult to section the cervix, which

had acquired a cartilaginous consistency, like a diffuse tumorous fibromatosis. On the scale used by Lipschütz and Vargas (14) for rating tumors induced by estrogen in the guinea pig, a small discrete tumor is rated 1.0 and a large tumor 3.0. For purposes of tabulation this fibrosis, being something less than a tumor, was rated 0.5. Such fibrosis is comparable with that reported in other animals given prolonged estrogen treatment, for example, by Lacassagne (7) and by Zuckerman (22).

FIG. 1. FIBROSIS IN THE FORM OF A KELOID PLAQUE ON THE FUNDUS OF THE STOMACH

Female rhesus monkey (no. 703) castrated, treated with estradiol 292 days. *a*, section × 4; *b*, section × 80.

Coming now to the mesothelial reaction, animal 703 exhibited a keloid plaque of fibrosis 20 by 6 mm. over the fundus of the stomach, that is to say, exactly in a place in which a fibroid reaction occurs in 35 per cent of guinea pigs similarly treated (fig. 1).

In addition, animal 730 showed a pronounced adhesive fibrosis at the site of the laparotomy, with fibrotic strands such as are seen in the treated guinea pigs. It should be recalled that all the animals were laparotomized when they were castrated, but only this animal 730, which had a second laparotomy while receiving an ample dosage of estrogen, showed such an operative fibrosis. This fibrosis was also evaluated at 0.5.

The results of the experiment are summarized in tables 1 and 2.

TABLE 1

General data and macroscopic findings

NO.	PERIOD TREATED	BODY-WEIGHT		WEIGHTS OF PELLETS		TOTAL ABSORPTION	CONTINUOUS ESTROGEN EFFECTS§	UTERINE BLEEDING	UTERINE WEIGHT	FIBROID RESPONSE*				REMARKS
		Start	End	Start	End					Uterus	Region of utero-tubal junction	Other viscera and abdominal wall	Spleen	
	days	*gm.*	*gm.*	*mgm.*	*mgm.*	*mgm.*			*gm.*					
729—I‖	69	3560		70.0	54.3	15.7	+	0		0	0	0	0	Found dead
730—I	285	3990	3370	80.0	†		+	0	9.0	0.5¶	0	0.5¶	0	Miliary abdominal tuberculosis. The fibrosis was at the sites of abdominal operations. Pellet was eliminated
185C—M	287		3570	101.3	29.0	72.3	+	0	11.0	0.5¶	0	0	0	
703—M	290	4840	5740	112.7	‡		±	0	4.7	0	0	0.5¶	0	Continuous estrogen effect only up to 200 days, when pellet was absorbed. The fibrosis was a keloid plaque over the fundus of the stomach

* According to the scale of Lipschütz and Vargas (14) (see text).
† Eliminated about 10 days before the end of the experiment.
‡ Not present at autopsy.
§ The estrogen effects recorded here are high color of sex skin and desquamation of vaginal epithelium.
¶ Fibrosis.
‖ I = immature; M = mature.

TABLE 2

Microscopic findings

NO.	VAGINA CORNIFICATION	CERVIX SQUAMOUS METAPLASIA	UTERUS		PERITONEUM, FIBROSIS	MAMMARY GLAND DEVELOPMENT
			Corpus, glands	Myometrium, fibrosis		
729	+	+++	Some normally differentiated glands	±	0	Very marked
730	+	+++	Some differentiation with cystic tendency	+++	+ (about abdominal scars)	Marked
185C	+	0	Discrete cystic hyperplasia	++	0	Slight
703	0, at end of exp.	0	Some normally differentiated glands	0	+ (on stomach)	Very little

COMMENT

As stated above and summarized in table 1, the only response in these monkeys in any way suggesting the fibromatous reaction in the guinea pig is a diffuse fibrosis of the myometrium in animals 185C and 730, a fibrotic reaction about the operative scar in no. 730, and a fibrotic plaque on the stomach of no. 703. The latter reactions, in fact, alone closely resemble lesions sometimes actually found in the guinea pig, for the fibrotic reactions of the myometrium are not much like the guinea pig tumors.

Lipschütz and co-workers have pointed out that in the guinea pig fibrosis is the minimal reaction to estrogen, indicating low susceptibility. The rhesus monkey seems therefore to be less sensitive to estrogen-induced fibroid changes than the guinea pig.

The effect of estrogen on the endomentrium is also quite different in the two species. In the guinea pig estrogens produce a very toxic effect on the endometrium, causing necrosis and sometimes pyometra. In the monkey, however, the endometrium is always maintained. The squamous metaplasia of the monkey's cervix is also exceptional in the guinea pig.

SUMMARY

In an attempt to produce estrogen-induced fibroid reactions in the rhesus monkey, under experimental conditions similar to those used by Lipschütz and co-workers in the guinea pig, 4 oöphorectomized monkeys were treated with estradiol in subcutaneous tablets.

Under these experimental conditions none of the animals showed fibroid tumors or disseminated miliary nodules. One exhibited a keloid plaque of fibrosis over the stomach, and another had pronounced operative adhesions and fibrosis at the site of the laparotomy. In addition two animals showed a pronounced fibrosis of the myometrium, particularly around the cervix uteri.

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STUDIES IN THE METABOLISM OF THE HUMAN PLACENTA

I. Oxygen Consumption in Relation to Ageing

H. W. WANG and L. M. HELLMAN

From the Department of Obstetrics, Johns Hopkins University and Hospital

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In general the process of ageing involves a slowing down of body processes. Accompanying this is an increase in the rate of degenerative change (katabolism) over that of repair (anabolism). This phenomenon is manifest not only in the organism as a whole, but also in the individual organs of the body, and even in their respective cellular elements. Certain aspects of ageing may be studied through observations on the alterations in the functional performance of the organ, others by changes in morphology, and still others by a study of the metabolism of individual cells. While all of these studies will in general show a progressive decrease in activity concomitant with ageing, no single approach can serve to give a picture of the complete process involved in growing old. Obviously, moreover, the physiologic activity of cells cannot be accurately ascertained from a study of fixed sections. Yet under the microscope cells show certain signs which in a general way indicate the state of metabolic activity which they were in as the tissue was fixed; namely by the presence of large vesicular nuclei, mitotic figures, cytoplasmic vacuoles, cytoplasmic projections, mitochondria, and in some instances the presence of fat in the cytoplasm.

Ageing of the human placenta may be a factor of great importance. The effect of this process on the child and on the mother is, at the present time, unknown. It is realized in a general sort of way that the placenta is an organ having a limited life span. During the short space of gestation all of the morphologic and metabolic changes, which in a human body take a lifetime, occur in this organ. The morphological changes have been accurately described and will be briefly outlined below. From the metabolic standpoint no studies have been carried out on human placentas, although in 1925 Murphy and

Hawkins (3) investigated the oxygen consumption of the placenta of the rat at term. It is, therefore, the object of the present study to determine the oxygen consumption of the human placenta at various stages of pregnancy, and to ascertain whether this bears any relationship to the changing histologic picture.

At twelve weeks (figure 1) the villi are large and covered with a double layer of epithelium. The outer, or syncytial, layer is made up of a continuous band of cells with indistinct or absent cell boundaries. On the external surface there are small irregular cytoplasmic projections resembling a "brush" border. The nuclei are large, rather regularly spaced, and the chromatin is vesicular. There are perinuclear cytoplasmic vacuoles and some fat. Mitochondria are numerous. The second layer that lies beneath the syncytium is known as Langhans' layer. It is made up of individual cuboidal cells with large round nuclei. Mitotic figures are present and also cytoplasmic vacuoles. The stroma of these young villi is very cellular, being composed of stellate fibroblasts with large nuclei. There are a few fetal vessels, but their endothelial nuclei are so large that they project into the lumina. No mitoses are visible but embryologically these cells are not far advanced beyond the time when they were capable of making red blood cells.

At 18 weeks' gestation a great change has taken place in the placenta (figure 2). The cells are smaller. Langhans' layer has disappeared and only isolated cellular remnants of it are seen. The nuclei in the syncytium are more compact, and tend to gather, forming so-called nuclear knots. The brush border has gone, and the process of ageing in these cells has led to breaks in the continuity of the lining of the intervillous spaces so that there is a tendency for fibrin to be deposited upon the villi. There are no vacuoles and the amount of fat is diminished. Mitochondria are difficult to find (Wislocki). In the stroma, too, the cells are more compact. Fetal vessels are more numerous and the endothelial nuclei less prominent.

At 29 weeks and at term, (figures 3 and 4), the change is even more marked. The villi become progressively smaller. The syncytial nuclei are small and pyknotic. They tend to gather in knots leaving the villi covered with an acidophilic membrane. The stromal cells are very few and quite small. A large part of the villus eventually

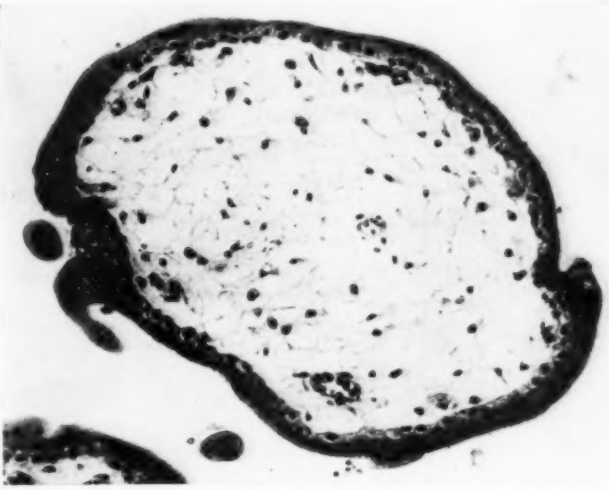

FIG. 1. HUMAN PLACENTA FROM 12 WEEKS PREGNANCY (× 100)

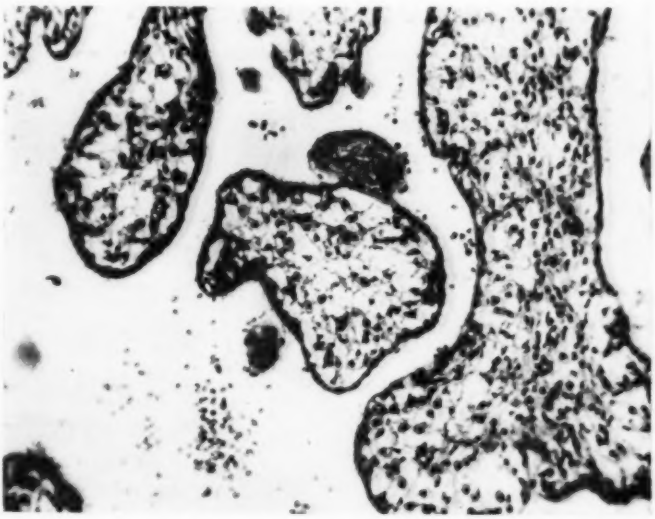

FIG. 2. HUMAN PLACENTA FROM 19 WEEKS PREGNANCY (× 100)

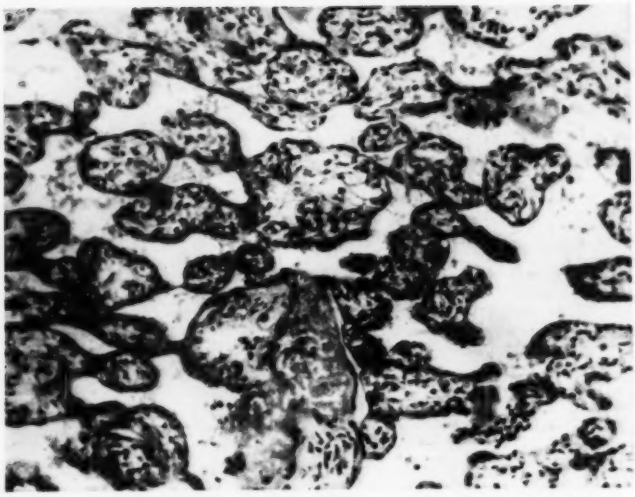

FIG. 3. HUMAN PLACENTA FROM 28 WEEKS PREGNANCY (× 100)

FIG. 4. HUMAN PLACENTA FROM 40 WEEKS PREGNANCY (× 100)

The villi are very small and numerous. They are covered with an acidophilic membrane containing unevenly spaced nuclear knots. The deposition of fibrin is marked. The stroma is almost entirely replaced by fetal capillaries.

becomes occupied by fetal capillaries. The latter have shown a progressive decrease in the cellularity of their walls, until at term the endothelial nuclei are few, flattened, and compact.

Thus, from a purely cytological aspect, one would hazard a guess that there is a progressive diminution in the metabolism of the villous cells with the advance of pregnancy.

MATERIALS AND METHODS

Term placentas of normal patients were obtained from spontaneous and operative deliveries. Premature placentas at different stages of pregnancy were secured from either spontaneous deliveries, or abdominal hysterotomies. The placentas of dead fetuses were excluded. The indications for hysterotomy were: pneumonia, tuberculosis, vaginal and rectal strictures, chronic hypertensive vascular or cardiovascular disease and chronic myelogenous leukemia.

The placenta was obtained always within one hour after delivery and in the majority of cases brought to the laboratory within 20 minutes after its removal at operation. A few small pieces of placental tissue were cut off and immediately placed in phosphate Ringer's solution. Areas of infarction, fibrosis or calcification were excluded. The small pieces of tissue were then prepared by cutting and teasing in the phosphate Ringer's solution until each tiny piece contained only a few villi. About 200–300 mg. of wet weight of tissue were used in each experiment and suspended in 2.5 cc. of phosphate Ringer's solution. Throughout the series of experiments the phosphate Ringer's solution of Dickens and Simer, with pH of 7.4, was used, except on 10 occasions when the glucose substrate solution was employed as a substitute. Either 1 mg. or 2 mg. of glucose were added to each 1 cc. of phosphate Ringer's solution.

All observations were made in the Warburg apparatus at a constant temperature of 37.8°C. and in an atmosphere of oxygen. The precautions given by Dixon (4) were followed. The readings were taken 10 minutes, 30 minutes, and 60 minutes after equilibrium was reached. When the experiment was completed the tissue was washed with distilled water and dried in an oven and weighed. The oxygen consumption is expressed in cubic millimeters of oxygen per milligram dry weight of placental tissue per hour.

OBSERVATIONS

Observations were made on mature as well as on premature placentas at different stages of pregnancy. As the mature placentas were readily available, while the premature ones were scarce, more observations have been made on the former. The average values are shown in Table I. The time interval between the delivery of the placenta and the test was not important if less than one hour. How-

ever, the values were much lowered, sometimes approaching zero, if the tissue was obtained longer than one hour after delivery.

TABLE I

Oxygen Consumption of Human Placenta at Different Stages of Pregnancy

DURATION OF PREGNANCY (MONTH)	NUMBER OF CASES	AVERAGE OXYGEN CONSUMPTION (C. MM. PER MG. OF DRIED PLACENTA PER HOUR)
2.0	1	5.3
3.5	3	4.7
4.5	3	3.8
5.0	1	3.7
5.5	1	3.7
7.5	2	3.3
8.0	3	3.3
8.5	4	3.2
Term	18	1.7

TABLE II

Influence of Chronic Hypertensive Vascular Disease on Oxygen Consumption of Placenta

	TERM PREGNANCY		3.5 MOS. PREGNANCY	
	Without chronic hypertension	With hypertension	Without hypertension	With hypertension
Average oxygen consumption of placenta...	1.7 (18 cases)	1.7 (2 cases)	4.3 (2 cases)	5.0 (1 case)

TABLE III

Influence of Analgesia and Anaesthesia on Oxygen Consumption of Term Placenta

TYPES OF ANALGESIA AND ANAESTHESIA	AVERAGE OXYGEN CONSUMPTION OF TERM PLACENTAS
None	1.7 (2 cases)
Nitrous oxide-oxygen and ether	2.0 (3 cases)
Seconal, paraldehyde, nitrous oxide, oxygen and ether	1.6 (10 cases)

Special attention has been paid to the oxygen consumption of the placenta in cases of chronic hypertensive vascular disease. The results indicate that this disease has no influence on the oxygen consumption of the placenta, as shown in Table II.

The effect of using analgesia and anesthesia during labor on the

oxygen consumption of placenta was also investigated. The full term patients were divided into three groups. The first group received no analgesia or anesthesia during labor. A second group received only a nitrous oxide-oxygen-ether mixture during the second stage. A third group received both seconal and paraldehyde during the first stage of labor, and nitrous oxide-oxygen-ether mixtures during the second stage. The barbiturate given was usually 0.3 grams of seconal. The amount of paraldehyde administered varied considerably. The maximum amount was 46 cc. The results of studies of these 3 groups are shown in Table III. It can be safely said that the oxygen consumption of the placenta is not influenced by the use of seconal, paraldehyde or nitrous oxide-oxygen-ether mixtures.

Observations were also made by suspending placental tissue in the glucose substrate solution, some containing 1 mg. and others 2 mgs. of glucose per 1 cc. of phosphate Ringer's solution. The average oxygen consumption of term placentas in the 1 mg. or the 2 mgs. of glucose per cc. of phosphate Ringer's solution was 1.9 and 1.8, respectively. In other words, the oxygen consumption of placentas in the three different solutions is within the same range, indicating that the addition of glucose to the phosphate Ringer's solution does not materially increase the oxygen consumption of this organ.

DISCUSSION

The oxygen consumption of the human placenta per unit weight decreases as the pregnancy advances, the value being lowest in the term placenta. This variation corresponds very well with the histological changes in the villi of the organ. Because of the close correlation between the oxygen consumption and the histological picture of the placenta, it is reasonable to assume that one of the important causes of the gradual decrease in oxygen consumption is the change in the chorionic epithelium with disappearance of Langhans' layer at the middle of pregnancy, and with some syncytial degeneration at term.

In cases of chronic hypertensive vascular disease complicating pregnancy the oxygen consumption of the placenta is not influenced. This may be explained on the basis of the essentially normal histologic picture of placentas in cases of chronic hypertension, as reported by Tenney (1, 2).

It is interesting to note that seconal and paraldehyde, as well as the nitrous oxide-oxygen-ether mixtures which were given to eight patients during labor did not depress the oxygen consumption of the placenta. Quastel and his collaborator (1, 6, 7, 8) have investigated the influence of various narcotics upon the oxygen consumption of brain tissue of various animals, while Zorn and his co-workers (9) have studied the effect of certain barbiturates upon the oxygen consumption of rat liver and brain. These authors demonstrated that narcotics, even at low concentrations, inhibit the oxygen uptake of the tissue studied. The inhibition became greater as the narcotic concentration was increased, or the period of exposure prolonged. But their experimental conditions are different from ours. They exposed the tissue to be studied directly to the narcotic *in vitro*, while in our experiments the placental tissue was exposed to analgesics or anaesthetics indirectly, that is, *in vivo*.

The oxygen consumption of term placenta does not increase in the presence of glucose in phosphate Ringer's solution. This may be due to a moderate amount of syncytial degeneration in the villi at term, making them unable to oxidize the glucose. Quastel and others (10) studied the oxygen uptake of brain and found that any profound change in cell structure would be reflected in a lowered oxygen uptake by the tissue in the presence of hydrogen donator as glucose.

SUMMARY

1. The oxygen consumption of human placentas at different stages of pregnancy was studied.

2. The oxygen consumption of the human placenta decreases gradually as pregnancy advances, a fact in keeping with the changing histologic picture of the organ.

3. The oxygen consumption of the term human placenta is not influenced by the use of analgesics or anesthetics during labor.

4. Addition of glucose into the phosphate Ringer's solution does not increase the oxygen consumption of the human term placenta.

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FURTHER OBSERVATIONS ON THE LOWERING OF BLOOD URIC ACID BY URICASE INJECTIONS

ELLA H. OPPENHEIMER AND HENRY G. KUNKEL

From the Department of Pathology, The Johns Hopkins University, Baltimore, Md.

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In a previous study (1), it was shown that a solution of the enzyme uricase, extracted from pigs' liver, when injected intravenously or intramuscularly into "gouty" hens, causes a sharp lowering of the plasma uric acid. Only a very crude uricase extract was used, and except for a single series at longer intervals, all observations were made one hour following single injections of the material. No attempt was made to observe the effect of prolonged or repeated uricase administration.

Because of the success of this early study, it was thought that further purification of the enzyme was indicated, as well as more elaborate studies of its *in vivo* effect. The earlier work suggested that, in hens, a single injection of the enzyme might produce uricolysis lasting 24 hours; yet a more accurate measure of the duration of the uricolytic action from a single injection was necessary to determine a proper interval of dosage for studying the prolonged effect of uricase administration.

In this present study, chickens—cocks as well as hens—were again used for the *in vivo* experiments. It is true that avian uric acid is derived from the protein of the food to a greater extent than from endogenous sources. The origin of the high plasma uric acid values in chickens, fed a high protein diet, therefore, is not analogous to that of the high plasma uric acid levels in human gout. Nevertheless, because of the ease of producing high uric acid levels by the simple means of feeding chickens a meat diet, these birds are ideal animals for testing *in vivo* uricolytic activity.

In selecting chickens for these experiments it was found that differences in weight or sex were unimportant, but the size of the wing veins facilitated or impeded the work. Most investigators in the past have made heart punctures to obtain chicken's blood, but we found that with large wing veins, frequent venipunctures were pos-

sible. Hematomata and thromboses occasionally made venipuncture difficult, but after several punctures, the vein and surrounding tissue became indurated and when pressure was immediately applied after removal of the needle, no further bleeding would occur.

Bollman and Schlotthauer (2) showed that in turkeys the blood uric acid rises after a meal, proportionately to the protein contained therein; and that the uric acid level falls while fasting. Similar observations were made by us in chickens, and due to some irregularity in feeding over certain week-ends, some minor fluctuations of uric acid levels did occur. During one period of observation, it was noted that if the chickens were fed once daily, as in the barnyard, the uric acid level varied according to the time after feeding. But this dietary fluctuation was eliminated by putting ground beef in the food pan twice daily, so that some meat was constantly available and the chickens could always pick at their food. In this way a fairly constant uric acid level was observed while the meat diet was utilized.

The total amount of meat consumed per chicken averaged about 8 ounces daily. Other variations in this diet were tried in an effort to provide the chickens with a satisfactory high-protein intake. For a short period meat, mixed with chicken feed and urea, was fed the chickens. This raised the uric acid to so high a level that it was no longer comparable to that found in gout. When urea was mixed with only chicken feed, the chickens could eat the feed, leaving part of the urea. Consequently there were again fluctuations in the uric acid determinations and the general uric acid levels were much lower than when the chickens were maintained on a meat diet. The meat diet, therefore, with water *ad lib.*, was the most satisfactory diet for our purposes.

For uric acid determinations, about one and a half cubic centimeters of blood were removed from a wing vein into an oxalated tube. Plasma filtrates were prepared by the method of Folin (3). However, instead of adding 0.5 cc. of 10 per cent sodium tungstate solution, 8 cc. of water and 0.5 cc. of $\frac{2}{3}$ N sulphuric acid separately to 1 cc. of the plasma, a stock solution of 1 part 10 per cent sodium tungstate and 8 parts N/12 sulphuric acid was made and 9 cc. of this solution was added to 1 cc. of plasma to precipitate the plasma proteins. If a smaller amount of plasma was obtained, a smaller amount proportionately of stock solution could be used with accuracy. After filtering off the plasma proteins, uric acid determinations were made on 5 cc. of the water-clear filtrate by the method of Benedict (4).

To prepare the uricase solution, a pig's liver was ground and extracted with acetone, and dried as for the crude extract of the earlier experiments. As it was noted that different pigs' livers yield varying amounts of enzyme, only those liver powders yielding markedly potent enzyme were used for further purification. Following Davidson's procedure (5) as our model, but adding a few minor variations of our own, we extracted liver powder to obtain a more highly purified product than was previously used for the work in our first report. As it was found that much uricase was lost along with the protein dissolved by Davidson's first extraction with M/10 phosphate buffer pH 7.4, this step was omitted, and M/10 borate buffer pH 10.0 extraction was made directly on the liver powder. After discarding all solid material, this borate extract was used for the crude uricase preparation. Then an equal volume of ice-cold saturated ammonium sulphate solution was added to the borate extract to precipitate the uricase, which was filtered off in the ice-box, and dissolved by shaking in ice-cold distilled water. This water solution of uricase was further purified by adding 1/10 volume ice-cold saturated ammonium sulphate and heating to 55°C. for 5 minutes. This caused the heavy precipitation of flocculent protein which was discarded by filtration. To the uricase containing solution, enough ice-cold saturated ammonium sulphate was added to bring the saturation to 50 per cent. This caused the precipitation of the uricase, which was filtered off and dissolved in ice water as before. After dialyzing this water solution of uricase in a cellophane sac for 18 hours in ice-cold distilled water, the resulting brown precipitate was extracted with M/10 phosphate buffer pH 7.4 to get rid of residual unwanted protein, and the remaining solid material was rubbed into solution in a mortar with M/10 borate buffer pH 10.0, using one tenth the amount that had been originally used for the first borate extraction. This solution formed our "pure" uricase extract.

In spite of using considerable care, and attempting no variation in technique except the omission of the phosphate buffer extraction on some materials, many extracts so prepared showed reduced uricolytic activity following purification and concentration, or no activity whatsoever, their potency having been lost at various steps in the process. It was therefore, with much gratitude, that we accepted uricase extract proffered us by Dr. Alexander Gutman and Dr. Bradley T. Scheer, who prepared and purified it in the Medical Department of Columbia University School of Medicine. This extract was made bacteria free before sending it to us, by filtration through a L2 Chamberlain filter, first saturated with alkaline buffer to prevent adsorption of the enzyme by the filter (6). It was sent frozen in dry ice, and on receipt it was stored in the refrigerator in sterile containers. Several lots of material were divided into sterile 1 cc. ampules, sealed with a vacuum, and after quick freezing stored at −28°C. This material retained its potency for over 2 months; it was not tested over a longer period as the supply gave out at that time.

The uricase extract prepared by Dr. Gutman and Dr. Scheer was obtained by a procedure similar to ours, but it was purified to a greater degree than the material prepared by us. Six guinea pigs were inoculated with this material as follows: 2 guinea pigs each were injected subcutaneously with 2 cc. of the material; 2 cc.

were injected intraperitoneally into each of another 2 guinea pigs; and 2 more guinea pigs received 2 cc. intravenously. After 3 weeks, all of the guinea pigs were given 1 cc. of the extract intravenously. None showed any manifestations of protein hypersensitivity.

EXPERIMENTAL

Four series of experiments were made to study various problems relative to the *in vivo* activity of uricase, as follows:

1) Experiments were conducted to determine if single injections of purified uricase extract would have the same effect as produced by the crude extract used in the earlier studies.

2) An attempt was made to determine the duration of the uricolysis following a single injection of purified uricase.

3) Experiments were made to determine the effect of prolonged and repeated uricase administration in "gouty" chickens.

4) Uricase administration was started in normal hens at the exact time of altering their diet to a "gout"-producing diet, to discover if this uricase administration would prevent the appearance of "gout".

Series I

In this experiment 7 chickens were used. All of the birds received a meat diet, with the meat continuously available; for part of the time urea was mixed with the meat. This accounts for the extremely high uric acid levels found in these chickens, all of which eventually developed "gout", with tophi in various positions in the legs and feet.

There were 24 determinations of the effect of injection of 1 cc. of purified uricase extract prepared in this laboratory; 2 injections were intravenous, but as intramuscular injection was much simpler technically and seemed to be just as efficacious, this method of injection was used 22 times. There were 13 control determinations following injection of 1 cc. M/10 borate buffer pH 10. In every instance, the chicken was bled immediately before injection and again one or two hours later, to determine the effect of the injected uricase or control material. During this interval, the birds were returned to their cages where their food was always available. The control chickens showed some slight reduction of uric acid, ranging from 0 to 16.8 per cent, or an average reduction of 4.5 per cent. On the other hand, the chickens receiving the purified uricase showed marked lowering of

the uric acid level after every injection of this material with the uricolysis ranging between 35.9 per cent and 79.9 per cent of the original plasma uric acid levels, or an average uricolytic action of 60.5 per cent. The results of the individual injections are shown in Table I.

Series II

In the second group of experiments, an attempt was made to determine the approximate duration of the uricolytic effect of a single injection of purified uricase in chickens fed a high protein diet. Until this experiment was begun, every injection of uricase in a chicken had been followed by the reduction of that chicken's plasma uric acid. In this period, however, numerous chickens showed no uricolysis following uricase injections, and these seemingly impotent preparations were always thought to be inactive and were discarded without using them again for further observations. In the light of later experiments, however, it now seems that these conclusions were erroneous. It is more probable that some outside factor may inactivate an active preparation of uricase, so that it is possible for the same material to produce uricolysis in one chicken and none in another. What this factor is remains unknown, and at present there is no clue to its nature.

Even though the observations following the negative results in some chickens were not completed, they are nevertheless included in Table II along with the observations indicating the uricolytic effect of a single uricase injection. It can be seen that there was a great variation in the duration of the uricolytic effect, undoubtedly modified in the longer periods of time by the chicken's appetite. The longest duration of the lowered plasma uric acid level following a single injection of 1 cc. purified uricase was in chicken number 45, in which it lasted over 70 hours. At 80 hours the uric acid was found at its pre-injection level. In 7 other series of observations, the uricolytic effect lasted over 20 hours, the uric acid having returned to its previously high level in 27 to 48 hours. In 4 hens, the uricolytic effect was demonstrated for only 4 to 6½ hours after the injection of uricase and the previous uric acid level was found in 8 to 19 hours. In 7 other chickens, uricolysis was demonstrated 2 to 3½ hours following uricase injection, but further observations could not be made because

TABLE I

Effect of Intramuscular Injection of Pure Uricase or Control Solution on the Plasma Uric Acid Level of Chickens Consuming a High Protein Diet

CHICKEN NO.	SOLUTION INJECTED	MGMS. URIC ACID PER 100 CC. PLASMA				PER CENT URIC ACID DESTROYED
		Before injection	1 hour later	2 hours later	Amount destroyed	
36	Uricase	26.7	8.9		17.8	66.7
36	"	22.9	7.3		15.6	68.1
41	"*	13.3	4.7		8.6	64.7
41	"	20.0	7.8		12.2	61.0
41	"	16.0	8.8		7.2	45.0
41	"	11.4		7.3	4.1	35.9
41	"	20.0	11.4		8.6	43.0
41	"	13.3		6.7	6.6	50.0
41	"	17.7		6.4	11.3	63.8
42	"	20.0	7.3		12.7	63.6
42	"	20.0	4.2		15.8	79.9
42	"	21.6	6.9		14.7	68.3
42	"	13.1	6.1		7.0	53.7
42	"	26.6	8.0		18.6	69.9
42	"	20.0		7.3	12.7	63.5
42	"	30.0	11.4		18.6	62.0
42	"	26.7		7.3	19.4	72.7
43	"*	28.6	9.4		19.2	67.1
43	"	32.0		10.0†	22.0	68.7
43	"	30.6	11.4		19.2	63.1
43	"	17.8		8.9	8.9	50.0
43	"	44.4	16.0		28.4	63.0
43	"	22.8		11.4	11.4	50.0
43	"	42.1		17.7	24.4	57.9
		Controls				
34	Borate	16.0	13.3		2.7	16.8
34	"	20.0	20.0		0	0
34	"	16.0	14.8		1.2	7.5
34	"	11.4	10.6		0.8	7.0
34	"	10.7		10.0	0.7	6.5
34	"	20.0	17.8		2.2	11.0
35	"	8.9	8.0		0.9	0.8
35	"	6.7	7.3		0	0
35	"	10.0	13.3		0	0
33	"	14.3	13.3		1.0	6.9
33	"	5.7	5.7		0	0
41	"	16.0	16.0		0	0
43	"	26.6	28.0		0	0

* Intravenous injection.

† 3 hours after injection.

of injury to the wing veins. In chicken number 3, there was no uricolysis at 6 hours, but a delayed effect was found at $10\frac{1}{2}$ hours after uricase injection, with a 47 per cent reduction of the pre-injection level of the plasma uric acid. The 17 injections of uricase that failed to produce uricolysis are added at the end of Table II.

Series III

In the third series of experiments, frequent uric acid determinations were made on 5 "gouty" chickens which had been fed a meat diet

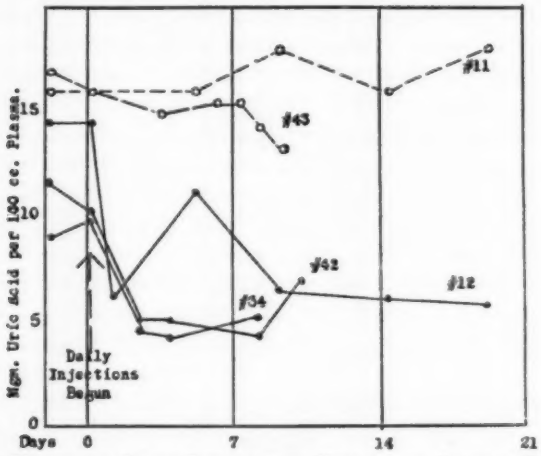

CHART I. EFFECT OF DAILY INJECTION OF URICASE OR CONTROL SOLUTION ON PLASMA URIC ACID OF CHICKENS CONSUMING HIGH PROTEIN DIET

Chickens #11 and #43 received daily control borate injections; chickens #12, #34 and #42 received daily uricase injections.

to produce a high plasma uric acid level. Several of these chickens had well-developed tophi. While receiving this diet, three of these chickens were given daily intramuscular injections of 1 or 1.5 cc. purified uricase. Chickens 34 and 42 received daily injections of 1.5 cc. uricase purified in this laboratory, while the purified uricase used for chicken 12, and given in daily amounts of 1 cc. was prepared by Dr. Gutman and Dr. Scheer. Two control chickens receiving the same high protein diet were given daily injections of 1.5 or 1 cc. M/10 borate buffer pH 10. The results are shown in Chart I. The control chickens showed a high level of plasma uric acid, which fluctuated

TABLE II

Duration of Uricolytic Effect on Plasma Uric Acid following a Single Injection of Uricase

HEN NO.	MGMS. URIC ACID PER 100 CC. PLASMA								DURATION OF OBSERVED URICOLYSIS
	Before injection	2–5 hours	6–9 hours	10–17 hours	18–24 hours	26–34 hours	44–70 hours	80 hours	
		After injection							
									hours
45	9.4				5.3	4.7	4.4	8.5	70
46	10.0		6.7		5.3	5.7	9.5		32
11	16.0	11.0			11.4		16.0		24
6	16.0				8.9	16.0			20
6	16.0				8.9				20
7	11.4				8.0	11.4			20
7	11.4				8.0				20
45	9.0	5.0	5.3		5.1	10.0			20
1	11.4		7.2		13.3				6.5
7	8.8		5.0		8.8				6.5
6	8.0	4.0		10.0					4
7	8.4	6.1		8.0					4
6	16.0	6.6							3.5
9	14.5	7.6							3.5
1	10.0		7.2						3
3	13.3	5.9							2
6	13.3	5.7							2
7	7.3	5.0							2
7	12.2	4.0							2
3	10.0		11.4	5.3					?10.5
6	8.0	11.0		10.0					0
6	13.3		13.3	11.4					0
6	20.0		22.0						0
12	15.0		14.0		20.0				0
11	16.0		16.0						0
7	11.1				9.5				0
1	16.0		15.0						0
7	11.4		16.0		13.0				0
2	28.0		28.0						0
5	20.0		22.8						0
3	11.4		16.0						0
8	17.7		20.0						0
41	8.0	8.8							0
6	10.0		10.0						0
41	10.0		11.3						0
3	13.0	12.3							0
6	8.0	10.0							0

very little, while the chickens receiving uricase showed a continued lowering of the plasma uric acid for the duration of the uricase ad-

ministration, which was for 7, 11 and 19 days. Their tophi, however, showed no reduction in size.

At the completion of this work, because of equivocal results reported to us by Dr. Gutman in chickens injected with uricase purified by him, another series of observations was made in 2 more chickens for a period of 2 weeks. The material used for injection was a new preparation of crude uricase which, *in vitro*, was shown to be very active.

As the preceding work indicated a continuous lowering of the uric acid level following daily uricase injections, these hens were given similar injections of 1 cc. uricase very day. However, they were tested frequently at 24 hours, just prior to the new injection, as well as 3 to 4 hours after the injections. In this way the prolonged effect as well as the immediate effect of the daily uricase injections could be observed. The plasma uric acid level of number 19, while consuming the high protein diet, was 12 mgm. per cent at the beginning of this experiment; number 15, which took the same diet showed an unusually low uric acid level with the value at 7 mgm. per cent. In the latter chicken, the first uricase injection produced no immediate uricolysis, although at 24 hours the level was lowered to 4 mgm. per cent. The second injection also showed no immediate uricolytic effect in this hen, but its uric acid level remained low throughout the period of observation, and later observations showed immediate uricolysis. Although daily uricase injections were given, observation of their effects was limited because of the amount of trauma to the wing veins.

The other chicken, number 19, showed uricolytic activity after the uricase injection, whenever tested, and the plasma uric acid level 24 hours after the last injection was always somewhat higher than the level 3 to 4 hours after. Following 8 days of uricase administration, the uric acid reading was 4 mgm. per cent, and at this point control injections of M/10 borate buffer, pH 10.0, were substituted for the uricase injections. A week later, the plasma uric acid was at the high level of 16.0 mgm. per cent. After making this reading, 1 cc. uricase was injected and 4 hours later the plasma uric acid was down to 8.8 mgm. per cent. The complete results are shown in Chart II.

Series IV

In the fourth experiment, only 4 chickens were used. For a period of 4 weeks they were allowed a normal chicken feed ration, and during

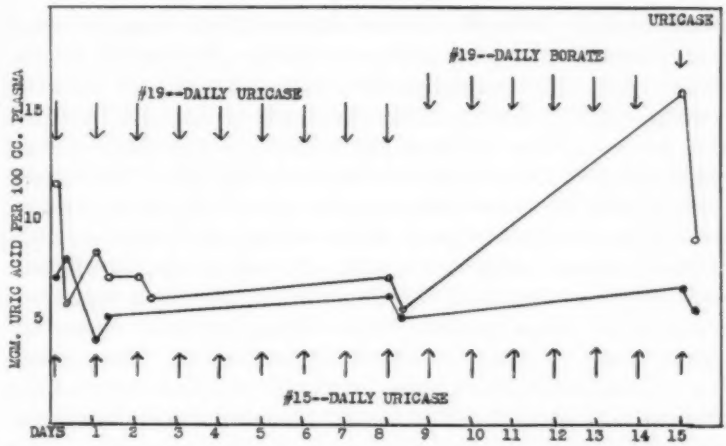

CHART II. IMMEDIATE AND PROLONGED EFFECTS OF INJECTION OF URICASE OR CONTROL SOLUTION IN CHICKENS CONSUMING A HIGH PROTEIN DIET

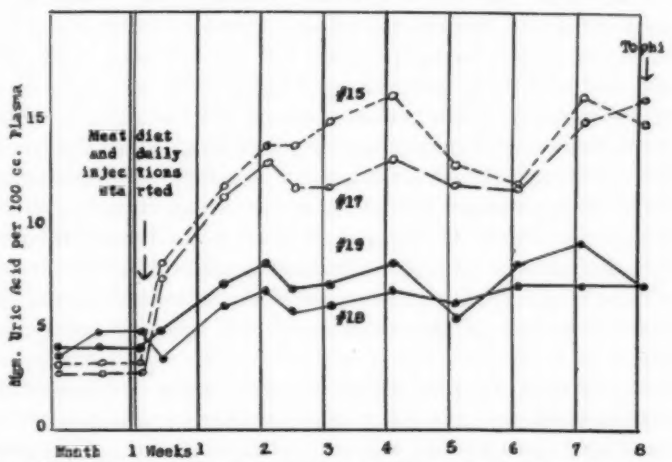

CHART III. EFFECT OF DAILY INJECTION OF URICASE OR CONTROL SOLUTION ON PLASMA URIC ACID OF CHICKENS CONSUMING A HIGH PROTEIN DIET

Chickens #15 and #17 received daily control borate injections; chickens #19 and #18 received daily uricase injections.

this time their plasma uric acid levels varied between 3 and 4 mgm. per cent. Then their food was suddenly changed to meat, or a "gout"-

producing diet. From this time on, chickens 18 and 19 each received a daily injection of 1 cc. of uricase, purified by Dr. Gutman and Dr. Scheer. This daily uricase injection was continued for a period of 8 weeks. During this time, chickens 15 and 17, acting as controls, each received a daily intramuscular injection of 1 cc. M/10 borate-buffer, pH 10.0. The results are shown in Chart III. The chickens receiving only the control buffer solution quickly showed a very high level of plasma uric acid, and chicken 17 had well-developed tophi at the termination of the experiment. In contrast, the two chickens receiving uricase injections, though constantly showing a higher uric acid level than when maintained on a normal diet, never reached the high or "gouty" plasma uric acid levels of the controls. Their plasma uric acid was always about 50 per cent lower than that of the control chickens. At no time during this experiment did they show tophi.

DISCUSSION

This series of experiments indicates that a solution containing a purified extract of the enzyme uricase, extracted from pigs' liver, when injected intramuscularly into "gouty" chickens with high plasma uric acid levels produced by a high protein diet, may cause a definite lowering of the plasma uric acid after a single injection. At times, however, the enzyme has not produced uricolysis after every injection, unknown factors causing failure of activity. The uricolytic action following a single injection of active uricase is prolonged and may last from 8 hours to well over 24 hours in chickens with a constantly available food supply. Irregular meals, or food given but once daily modifies this effect because of the added influence of the normal fluctuations in the plasma uric acid following eating and fasting.

Daily injections of purified uricase in "gouty" chickens will maintain their plasma uric acid at a much lower level than that of the control "gouty" hens receiving only injections of borate buffer. This effect lasts during the entire period of daily uricase administration, although the chickens are fed nothing except a "gout"-producing meat diet. However, no alteration in the size of tophi was observed during the limited periods of observation described in these studies. Similarly if daily injections of purified uricase are given to chickens with a low

plasma uric acid, at the same time altering the diet to a high protein diet, the plasma uric acid rises, but never reaches the "gouty" level of the control chickens receiving only daily injections of borate buffer. In other words, uricase has both reduced and prevented a "gouty" level of plasma uric acid in chickens.

This does not mean that a similar effect can be expected in man. Chickens are small and the uricase dosage is large per kilo of body weight. None of the birds weighed over 2 kilograms so that the minimum dosage was 0.5 cc. per kilo of weight per day. Smaller doses were tried with equivocal results, so that 1 cc. was the standard dose used, irrespective of the variation in the weights of the chickens.

Naturally, curiosity has been aroused as to the effect of uricase administration in man. That the enzyme can be purified for human usage has been demonstrated by the material prepared by Dr. Gutman and Dr. Scheer. Their preparation was made bacteria-free by filtration through a L2 Chamberlain filter. It is apparently not anaphylactogenic for guinea pigs; it can be stored in vacuum ampules, and it will maintain its activity when frozen for long periods of time.

Near the conclusion of this work, a man with gout was admitted to the Diagnostic Clinic of this hospital. Through the kindness of Dr. Charles W. Wainwright, this man was made available to us for study. His symptoms of gout had been present off and on for 12 years; for 4 weeks prior to admission painful joints had again distressed him. His plasma uric acid, even when he received a purine-free diet fluctuated between 5.7 and 6.9 mgm. per cent. He weighed 79 kilograms. As he had had no recent medication of any kind, it was decided to see if uricase, injected intramuscularly, would modify his symptoms or the plasma uric acid. Only 17 cc. of pure sterile uricase was available for administration. This was part of the supply given to us by Dr. Gutman and Dr. Scheer. Although this amount of uricase was small, we nevertheless injected it intramuscularly, cautiously, with no adverse effect whatsoever. For 3 days the patient received 1 cc. three times daily; the last day 8 cc. were given in 4 injections of 2 cc. each. There was no untoward reaction, local or general. Nor was there any lowering of the plasma uric acid which fluctuated between 6.2 and 7.2 mgm. per cent, or at a slightly higher level than before. There was also no amelioration of the pain or swelling in the gouty joints.

No conclusions can be drawn from this single attempt to study the effects of uricase administration in a patient. The dosage utilized was far too small per kilogram of body weight to produce any effect, if the experiments on chickens can be interpreted with reference to man.

For human administration it will be necessary to concentrate uricase considerably. In its present form the tremendous doses of this enzyme needed before any uricolytic results can be expected make its administration impractical. Meanwhile the fact that 17 cc. of purified uricase has been injected in a man with no untoward effects seemed worthy of record.

It would also seem important to study further the cause of the failure of the enzyme to produce uricolysis when injected in some chickens. At the present time, no explanation can be offered. However, because of the lack of any uricolytic effect after injection of control material, as well as the many positive observations of the prolonged uricolytic action after uricase administration, there is sufficient basis for continued attempts to purify and concentrate this enzyme.

CONCLUSIONS

1. The enzyme uricase can be extracted in a purified state from pigs' liver. A solution in M/10 borate buffer, pH 10, provides a satisfactory medium for intramuscular injection. This solution can be made bacteria-free by filtration, and it has not produced protein hypersensitivity in guinea pigs. It will remain active for at least 2 months when frozen and stored at −28°C.

2. Single injections of this purified uricase extract can produce a sharp lowering of the plasma uric acid of "gouty" chickens. At times, however, factors not yet understood cause failure of the activity of this enzyme *in vivo*.

3. Continued daily administration of uricase to "gouty" chickens made "gouty" by a high protein diet, causes a continued lowering of their plasma uric acid, although they are maintained on the same "gout"-producing diet.

4. Continued daily administration of uricase prevents the plasma uric acid level from rising to a "gouty" level in chickens simultaneously fed a "gout"-producing diet.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in the Hurd Memorial Hall, May 17, 1943

I. The Minimal Pathological Findings for the Diagnosis of Early Carcinoma of the Cervix. Drs. Richard W. Te Linde and Gerald A. Galvin

SUMMARY

Eleven cases of early invasive carcinoma of the cervix, diagnosed preoperatively by biopsy specimens and treated by panhysterectomy were presented. The diagnosis in each case rested solely upon the recognition and correct interpretation of abnormal changes in the surface epithelium in the biopsy specimens as these specimens failed to show the stromal invasion of malignant epithelium. The constant findings in the surface epithelium of these biopsies were hyperactivity of the basal cells with the presence of anaplastic nuclear changes and the loss of normal stratification. In all cases the cervices removed at operation, when sectioned completely, showed unquestionable yet very early invasive carcinoma of the cervix. The microscopic findings in the biopsies as well as those in the removed cervices were demonstrated by means of photomicrographs.

In none of these cases could the diagnosis be made clinically nor was there any gross evidence of malignancy in the cervices removed at operation. The indication for the taking of biopsies in these cases was the presence of minute leukoplakic or granular areas on the cervix or merely the history of irregular vaginal bleeding.

The object of the study was to correlate the biopsy findings with the findings in the specimens removed at operation and thus to discover the minimal epithelial changes required in a cervical biopsy to justify the diagnosis of carcinoma. The study also served to emphasize the importance of the cervical biopsy and its correct microscopical interpretation.

DISCUSSION

Dr. Emil Novak: The findings in the group of cases presented by Dr. Galvin are very instructive. The fact that such a number of very early cases of cervical carcinoma could be collected in a relatively short time is a good indication of the alertness of the staff and the thoroughness of the study in this group.

The chief lesson to be drawn from this series is that in every case the complete study showed early but unquestioned carcinoma, although the biopsy sections showed no evidence of the invasion which some look upon as essential for diagnosis. As a matter of fact, when the biopsy shows typical so-called preinvasive carcinoma, further study may show even fairly extensive carcinoma in the near vicinity, for a zone of preinvasive or intraepithelial carcinoma may constitute the growing margin of even advanced cancer. Many years ago the late Dr. Erwin Smith, a well-

known plant pathologist, spent some time in studying sections in our laboratory from this standpoint, having observed that in malignant plant tumors there was a similar lighting-up, so to speak, of the surrounding epithelium. This does not, of course, mean that the surrounding epithelial cells are transformed into cancer cells, but rather that they are replaced by the advancing cancer epithelium.

When a biopsy shows only the preinvasive picture, one of two possibilities is to be considered. In the very occasional case—and we have had only a small group of these—even the most complete serial study of the cervix shows no invasiveness at any point, and it is these rare cases which have led to so much discussion as regards their later potentialities. Apparently they represent the prodromal phase of cancer, but a long lag of even many years may elapse before the second and distinctive invasion brings about an outspoken cancer.

Far more frequently, however, the finding of preinvasive cancer in the biopsy indicates the proximity of a typical invasive carcinoma, and further study will unearth this, as in the cases reported tonight. All of which emphasizes that biopsy is a real art, that it does not consist merely in the study of a routine section taken at random, and that it is our most valuable means for establishing the diagnosis of early carcinoma.

Dr. George O. Gey: My interest in carcinoma of the cervix began about twenty years ago when Dr. Carl Henry Davis reviewed some of his cases at Columbia Hospital, Milwaukee. I had an opportunity to study and photograph some of these and one of them is shown here (lantern slides) because it is a very early lesion and shows well the growing edge of tumor cells which appear to be "invading" the adjacent normal cells. Following the study of this section, I have never been satisfied that the lesion shown here is one that shows the destruction of normal cells by tumor cells; more probably this is an instance of what Dr. Novak just now called a "lighting-up" process, which implies that the malignant cells which are in contact with the normal cells of the same cytogenic origin actually cause the normal cells to become malignant.

This is an academic question which may not be of very great interest to most clinicians but to those interested in experimental carcinogenesis it is of fundamental importance. The only report that I can recall at the moment that deals with this point is that of Brunschwig and Tschetter who have described quite well the zones of continuity between cancerous and non-cancerous (hyperplastic) epithelium and between cancerous and frankly normal epithelium in several types of early carcinoma. Ribbert, a long time ago, wrote about this cancerization by adjacent cells as a factor in spread by contact, but thought it highly improbable. Ewing did not believe that such a process could occur. In our tissue culture work we have had the great fortune to observe what we believe is the first evidence for progressive transformation of normal into tumor cells. Two transformations were observed in strains of normal rat mesenchyme that have been maintained for a number of years.

Usually in sections of carcinoma of surface epithelium one sees much "round cell" infiltration beneath and between the tumor cells and often also between and

beneath the adjacent normal cells. Dr. W. H. Lewis and I were able to show, and reported long ago, that in many tumors these cells are macrophages which proliferate rapidly when tissue cultures are made of the malignant tissue. Many macrophages can be seen in the early carcinoma shown in this slide (lantern slides) from a case of Dr. Cullen's (No. 169) (1894) and illustrated in his book. Dr. Cullen also refers to "suspicious changes" in the normal cells at the outer margins of the early carcinoma. The presence of many phagocytic cells makes a detailed study of very early malignant lesions difficult to interpret. I have a few other slides of carcinoma of the cervix, kindly loaned me from Dr. Te Linde's service, which show quite well the juncture between normal and malignant cells (lantern slides). In these one does not see any evidence for the contention held by some that the tumor cells are able directly to destroy the normal cells which are seen adjacent to them. In these sections the normal cells show some increase in activity with an increase in the number of dividing cells. Whether or not these active normal cells can be induced to become malignant by the presence of neighboring cancer cells is a question difficult to answer from the study of slides alone. A similar problem is presented in these slides of Paget's carcinoma of the nipple and in these slides from cases of Bowen's disease. In Bowen's disease the "suspicious" areas may persist for many years without changing into cancer requiring clinical treatment.

Dr. Te Linde: We have been astonished by the frequency with which we have found these early cases of carcinoma. Eight of these cases were encountered in our laboratory in the past year and we are forced to consider whether we missed some in earlier years. I am sure we have overlooked some but the greatest reason for finding an increased number of these cases is the increased frequency with which we have taken biopsies in the past year or two.

The frequency with which we have found these lesions in normal or almost normal looking cervices causes us to reconsider the question of total versus subtotal hysterectomy. We have always been rather conservative in our attitude toward panhysterectomy but I must confess, in the light of these findings we have possibly been too conservative. Certainly the burden of proof lies upon the shoulders of the operator who wishes to conserve a cervix that is in the least suspicious. He must biopsy and if suspicious he must biopsy again until he is satisfied that malignancy has been ruled out.

Another interesting clinical fact is that the average age of these 11 patients was 36 while the average age for cervical cancer in general is 48 years. This is a very small series, of course, but this difference of 12 years makes one wonder how long such lesions can persist on the surface before developing into invasive cancer. We have two cases in our laboratory that are extremely important in relation to this. In one, a change in the surface epithelium, similar to that shown in these cases by Dr. Galvin, was found accidentally in the laboratory in a piece of cervical tissue removed in doing a trachelorrhaphy. No treatment was instituted. Eight and one-half years later the woman appeared in the clinic with an inoperable cervical

cancer. The cervix of the other woman was biopsied and similar changes were found in the surface epithelium. She refused treatment. Three years later she died of pernicious anemia. She had had no symptoms of cervical carcinoma prior to death. A complete biopsy was not obtained but the cervix was removed for study. The entire cervix was covered with epithelium showing the changes of which we have been speaking tonight. On the posterior lip definite invasive cancer was found.

We have not discussed the treatment of these microscopic lesions. We do not believe there is sufficient data to permit one to be dogmatic as to the superiority of irradiation over surgery or vice versa. It is my guess that almost all of them could be cured by either method. We have chosen surgery for two reasons: (1) in order to have the specimen for study to substantiate our diagnosis; and (2) in order to obtain a series to follow so that we may be able to form an opinion as to the efficacy of surgery. We are practicing the deliberate saving of an ovary in the young women since it is a site only of late metastasis of cervical cancer. If this can be successfully done it will prevent an early menopause, a decided advantage over irradiation.

II. Clinical Observations on Peripheral Nerve Injury and Regeneration. Dr. Curt P. Richter and David T. Katz

SUMMARY

In peace times peripheral nerve lesions are relatively uncommon and are confined almost exclusively to the upper extremities; in war times, however, they are so common that they constitute a large part of the casualties and they involve the lower quite as often as the upper extremities. Wars have always stimulated interest in peripheral nerve injuries and treatment. During World War I, 14–16 per cent of injuries to the extremities in base hospitals showed injury of peripheral nerves. This represented 4.5 per cent of the total casualties.

In the past the neurosurgeon had to limit his examination to changes in motor and sensory systems, both of which necessarily depended not only on the willingness of the patients to cooperate, but also on their ability and training to observe their sensations. In order to supplement or to replace information obtained from these sources, neurosurgeons have at various times made an effort to measure changes in autonomic functions, circulation, or sweating, which do not depend on the patient's cooperation. Some have made observations on the presence or absence of visible sweating. This was found to be useful only in a few patients with extremely active sweat glands. Others have used the Minor Starch Iodine test for sweat gland function which gave better but still not satisfactory results. In this test the skin is painted with a mixture of castor oil, alcohol and iodine and is then dusted with a rice powder. The moisture of the sweat turns the starch black leaving the affected areas white. However, it gives poor outlines of affected areas, requires much time and effort on the part of the examiner as well as of the patient, and has to be used only in special places equipped with showers, etc.

A new method which we have been using now for several years to map areas affected by sweat gland paralysis largely overcomes the shortcomings of the previous methods. It depends on the increased resistance offered by the skin to the passage of a minute direct electrical current when the cutaneous nerve supply is interrupted. For this work we use a small portable dermometer and two zinc electrodes. One electrode is fastened to the lobe of an ear with a small clip, while the other is held in the hand of the examiner and can thus be touched to the skin on any part of the body. The ammeter records areas of high or low skin resistance.

Some of the underlying principles which have come out of previous studies are, (1) the resistance offered to the passage of a minute direct current through the body is localized almost entirely in the skin. A puncture made through the skin with a fine hypodermic needle reduces the resistance at once from any level however high, even several millions of ohms, to practically zero; (2) skin resistance depends largely on nervous control. Section of the entire nerve trunk or of the sympathetic nerves greatly increases the skin resistance.

We have examined 27 patients with total or partial ulnar nerve lesions; 20 patients with radial nerve lesions; 16 with median nerve lesions; 6 with peroneal nerve lesions; 6 with lesions of the medial antibrachial cutaneous nerve; 6 with brachial plexus lesions; 4 with sciatic nerve lesions; and 3 with tibial nerve lesions.

In these patients we were able to map the affected areas and to follow the progress of regeneration of the sutured and unsutured nerves. Immediately after nerve injury the areas of high electrical skin resistance and areas of anaesthesia coincide. During regeneration the shrinkage of areas of high skin resistance precedes the shrinkage of areas of anaesthesia, thus indicating that sympathetic nerve regeneration precedes by a considerable interval the regeneration of the sensory nerves.

The unique advantages of the skin resistance test lie in the following factors: (1) It can be used directly at the bedside or in the field and requires little time or equipment. (2) It can be used in the presence of severe shock, or muscle, tendon or joint trauma when performance of the classical sensory and muscular tests is impossible. (3) It is objective, being independent of the patient's mental status and tendency to malingering. (4) It enables the discrete front of nerve regeneration to be detected within ⅛ inch. With combination of the sensory, motor and sympathetic nerve examinations the neurosurgeon should be able immediately after the injury to make a more accurate judgement of the location and extent of the lesion and also should be able to obtain a quicker estimate of the effects produced by various forms of therapy, nerve suture, grafting, etc. on the regeneration of the nerves.

DISCUSSION

Dr. Longcope: Is there a parallel change in skin resistance and in sweating as improvement takes place?

Dr. Richter: Yes, just about parallel.

Dr. Alfred Blalock: The members of the Department of Surgery are very grateful

to Dr. Richter and his associates for helpful advice in the treatment of patients with peripheral vascular disease and with peripheral nerve injuries. Always in time of war there is an increase in the number of nerve injuries. Unfortunately the injuries are sustained under such circumstances that nerve suture cannot be carried out at the time, and one has to resort to secondary suture after suitable delay. This fact increases the importance of observations such as Dr. Richter has reported, since the method described allows one to attain a better idea as to the extent of nerve injury.

There have been several important advances in recent years in the treatment of patients with nerve injuries. Dr. Weiss of Chicago has recently described the results of experiments in which the injured nerve is placed in a sleeve of artery. Fluid forms between the nerve ends and this is believed by Dr. Weiss to aid in the regeneration of the nerve. Furthermore, he has used auto- and hemo-transplants of frozen desiccated nerves in those instances in which the nerve ends cannot be approximated because of loss of substance. His experiments have been performed on small animals and it remains to see whether or not they apply to man.

Dr. Dandy recently published a report in the Journal of the American Medical Association in which he described the results in two patients who had lost a considerable length of nerve at the time of injury. Since he was unable to approximate the nerve ends, he shortened the arm of each of these patients by removing a part of the humerus. This allowed the nerve ends to be sutured.

Dr. Bodian has recently described a very ingenious method for bridging the gap in nerves. A clinical trial of his method appears to be indicated.

III. The Clinical Implications of Magnesium Deficiency. Dr. Maurice Sullivan and Virginia Evans

SUMMARY

When young rats are fed an otherwise adequate diet which contains insufficient magnesium there develops a disease characterized by hyperexcitability, tonic-clonic convulsive seizures, cardiac arrhythmia, tachycardia, nephritis, hepatitis, vasodilatation, intense generalized erythema and edema of the skin, erythema multiforme, dermatitis, thickening of the skin, hyperextensibility of the joints, edema of the dependent parts and finally nutritive failure, and death. Magnesium deficiency in calves results in the deposition of calcium salts in the yellow elastic fibers of the endocardium, of the aorta, jugular vein and larger arteries, of the surfaces of the diaphragm and of the trabeculae of the spleen.

Clinicians generally have lacked interest in magnesium deficiency and have neglected to explore the possibilities of its clinical significance. The clinical implications suggested by the experimental syndrome include tetany (Kruse, Orent and McCollum), epilepsy (Hirschfelder and Haury), arteriosclerosis (Moore, Hallman and Sholl), nephrosis (Greenberg, Lucia and Tufts), and disseminated neurodermatitis (MacCardle, Engman and Engman). A study (Dines and Lavietes) of the ultrafilterable and bound magnesium in the serum of normal patients and of

patients with hypothyroidism and hyperthyroidism showed that the total magnesium values in the three groups were similar, but in hyperthyroidism there was a great increase in bound magnesium in contrast to an almost total absence of bound magnesium in hypothyroidism. In other words, in hypothyroidism the magnesium was all ultrafilterable. These findings indicated an important interrelationship of magnesium and the thyroid hormone. Hirschfelder determined the blood magnesium values in many patients and described two conditions which he designated as 1) hypermagnesemia and 2) hypomagnesemia. The syndrome of hypermagnesemia was accompanied by somnolence and coma. It was induced in patients with renal insufficiency by the oral administration of one or more purgative doses of epsom salts. The syndrome of hypomagnesemia was accompanied by muscular twitching or convulsions, and when it occurred in patients with renal insufficiency the twitchings or convulsions were relieved by the oral administration of epsom salts.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Essentials of Gynecology. By WILLARD R. COOKE. 474 pp. Illus. $6.50. J. B. Lippincott Company, Philadelphia, 1943.

The object of the book as stated in the preface, "is to present concisely, from the practical viewpoint, and with as much correlation as possible, the salient features of the anatomy, pathology, symptomatology, and therapy of gynecology." The author has accomplished these objectives quite satisfactorily. The book is primarily for medical students. Although the author states in the preface that he has presented different viewpoints on controversial subjects, actually the book represents chiefly his own views or his interpretation of other opinions. No bibliography is given.

The author gives due recognition to the importance of gynecological pathology and enough space is devoted to this subject to allow the medical student to become acquainted with pathology sufficiently to enable him to understand symptomatology and treatment. It is a satisfaction to note that the author recognizes the importance of the study of psychology and personality in gynecology. Hence, he devotes a chapter to the patient herself, who is all too often neglected by many surgically and endocrinologically minded gynecologists.

The chapter on operations is, in the opinion of the reviewer, of questionable value. The major points of standard operations are outlined step by step, briefly and without illustrations. The reviewer can see little object in burdening the undergraduate student mind with steps in operative technique and surely the embryo gynecological surgeon could not learn operative technique by means of such scanty and unillustrated outlines.

The book is published in a very legible form and the pictures are well reproduced. Many of them are very simple sketches, doubtless made by the author himself, but they are clear and illustrative of the point to be made.

Taken as a whole the book is a very satisfactory text for medical students. One of its greatest virtues is its clear and concise form.

R. W. Te L.

Chemotherapy of Gonococcic Infections. By RUSSEL D. HERROLD. 137 pp. $3.00. The C. V. Mosby Company, St. Louis, 1943.

This useful book is a concise, understandable statement of the diagnosis and management of gonorrhea in the adult male. Short chapters are included on infection in women and in children. Only those features of bacteriology, pathogenesis and pathology are included which bear directly upon diagnosis and treatment.

Since most patients with gonorrhea come under the care of general practitioners, for whom (and medical students) this book is primarily written, the urologic aspects of management seem to be over-emphasized. The author, a trained urologist, no

doubt finds the recommended procedures useful. The average and less expert reader may feel that he too is capable of using the same tactics, with disastrous results to the patient.

Accurate diagnosis of gonorrhea is as important now as in pre-sulfonamide days. The history should include data on previous infections, present illness, sexual contacts and previous treatment for this infection. Physical examination consists of a search for signs of gonorrhea and its complications, two glass test and serologic test for syphilis.

Laboratory procedures are described, with techniques for collection of specimens of urethral exudate, urine sediment and prostatic fluid. The importance of cultures is stressed, but the author also outlines the course to be taken by those to whom cultures are not available. Staining of smears by Gram's method is insisted upon.

Sulfathiazole is the drug now used routinely by the author. He believes that proper dosage has not been accurately determined, but that 4.0 grams daily for five days cures at least 80 per cent of new infections in the male and is a satisfactory scheme of treatment.

The author states: "There may be some question of the actual additional value of local treatment in connection with chemotherapy. We are convinced that it is a definite aid in obtaining cooperation of patients. It is preferable, however, that no treatment be given unless by those experienced in such therapy. It is not necessary that self-treatment be permitted. . . . ". The technique and solutions used are described.

Management of sulfonamide failures is outlined according to whether the failure is associated with local complications or is the result of resistant organisms.

Procedures for determination of cure in different types of patients are outlined.

Sixty-two illustrative case histories are presented.

N. W. G.

Psychosomatic Medicine. By EDWARD WEISS and O. SPURGEON ENGLISH. 687 pp. Illus. $8.00. W. B. Saunders Company, Philadelphia and London, 1943.

This textbook represents the result of a collaboration from the points of view of internal medicine and psychiatry. The emphasis is upon treating sick people rather than their diseases. There is a tendency to oversimplification in the presentation of many of the psychosomatic concepts. Thus the "important" psychological meaning of cardiospasm is stated in the phrase "I can't *swallow* that situation". In the cases of ulcerative colitis, the physical and emotional immaturity of the individual is stressed. There are no exceptions to be found in the body of the text. All of the cases of peptic ulcer are characterized by a "regression" to the early stages of emotional life and manifest a strong desire for dependence upon others.

There is included an excellent review of the literature dealing with psychosomatic medicine. As a pioneer effort the book is more than praiseworthy. It is worth-while reading for everyone who is interested in the patient as an individual.

J. H. C.

Synopsis of Diseases of the Skin. By RICHARD L. SUTTON and RICHARD L. SUTTON, JR. 481 pp. $5.50. The C. V. Mosby Company, St. Louis, 1942.

This little book is designed for the beginner in Dermatology. It is small and can be carried in the coat pocket. For a book of its class, it is rather expensive. The arrangement of material follows fairly closely the authors' larger treatises. The subject matter is very complete and all-inclusive, and the etiological approach to diseases of the skin is more manifest than in older texts. Descriptions and discussions of individual diseases are concise, practical and well illustrated. The section on syphilis has been expertly reviewed with due regard to modern clinical conceptions and accepted methods of treatment. Attention should be called to the radical departure from common practice in the management of the patient with acne vulgaris.

H. H. H.

Advances in Internal Medicine. Vol. 1. Edited by J. MURRAY STEELE [and others]. 292 pp. Illus. $4.50. Interscience Publishers, New York, 1942.

This is the first volume of a series of reviews of current topics in internal medicine. The Editor believes that "the material selected as evidence for progress should be presented from the point of view of a particular individual—preferably one who has contributed to the advances of which he is to write . . . . ." This purpose would seem to be the primary motive for offering articles which necessarily duplicate in part reviews supplied in various medical journals. Many of the essays, notably several concerning problems of therapy, admirably fulfill their avowed mission.

A. B.

Bronchiectasis. By JAMES R. LISA and MILTON B. ROSENBLATT. 190 pp. Illus. $4.00. Oxford University Press, London, New York (etc.), 1943.

In this book a pathologist and clinician have compiled the important data on bronchiectasis, from the literature and their own experience, in a comprehensive and convincing way. The result is a very valuable work, bringing one up to date on all the current trends of thought concerned with this disease and serving as an excellent source of reference. A generous amount of space is allotted to discussion of the anatomy and histology of the broncho-pulmonary tree as well as to its physiology and the pathological changes reported by others.

The chapter dealing with the pathological findings in the cases of the authors is most complete and deals with the important early changes, so often overlooked in descriptions of the far advanced condition. The histological findings in cases of bronchiectasis associated with bronchial obstruction from any cause give ground for their thesis that the determining force in the pathogenesis is a destructive inflammatory reaction in the walls of the bronchi rather than any mechanical dilating factors.

The chapter on treatment is a brief one, but rather optimistic in its description of the surgical results. The authors contend that bronchiectasis is a chronic disease

which shows no tendency to heal spontaneously and can be eradicated only by surgical resection. While this attitude may be justified when applied to the fully developed chronic case, we feel that one may, at times, make the diagnosis early, before fibrosis has taken place, and that in these cases there is a chance of helping bring about cure with conservative treatment.

The book on the whole is very well arranged, and the various phases of bronchiectasis are discussed in a critical way; the bibliography is very comprehensive.

A. M. F.

Physical Chemistry for Students of Biochemistry and Medicine. By EDWARD STAUNTON WEST. 368 pp. Diagrams. $5.75. The Macmillan Company, New York, 1942.

This textbook should prove of interest and value to the average medical student who requires orientation and instruction in some of the elementary aspects of physical chemistry. Its primary object "is to present the selected phases of physical chemistry recognized as basic to an understanding of biological phenomena."

The scope of the work is indicated by the chapter headings: the structure of matter, and some fundamental chemical principles; gases and solutions; osmotic pressure; electrolytic dissociation and the mass law; acids, bases and buffers; the determination of pH; the colloidal state and membrane phenomena; oxidation and reduction; the velocity of reactions. These topics are simply and lucidly presented, some of the features being discussed in much detail. The last chapter is rather brief and might usefully have included more than a brief mention of enzyme kinetics.

B. C.

Introduction to Organic and Biological Chemistry. By L. EARLE ARNOW and HENRY C. REITZ. 736 pp. Illus. $4.25. The C. V. Mosby Company, St. Louis, 1943.

This elementary text will doubtless enjoy a deserved popularity since it appears to fill a long felt need. It covers the subject matter indicated by the title in a simple, logical, lucid manner. It is well written, well illustrated, and the format is good.

The fact that the text is replete with up-to-the-minute information drawn from many fields, particularly from industry, should make it interesting and valuable to many groups of technical workers as well as to the scientist and the layman.

The relative absence of the physico-chemical and mathematical approach to the subject will be as much condemned by some as it will be appreciated by others. For the student who does not think readily in mathematical terms this text should be a welcome source of factual information.

As often happens with first editions, a number of errors have crept into the text. These will not detract seriously from the excellent pedagogy.

M. V. B.